

**IN THE UNITED STATES DISTRICT COURT  
DISTRICT OF DELAWARE**

NIPPON SHINYAKU CO., LTD., Plaintiff,	)	
	)	
v.	)	
	)	C.A. No. 21-1015 (GBW)
SAREPTA THERAPEUTICS, INC.,	)	
Defendant.	)	
	)	
SAREPTA THERAPEUTICS, INC.,	)	
Defendant and Counter-Plaintiff	)	
	)	
v.	)	
	)	
NIPPON SHINYAKU CO., LTD. and	)	
NS PHARMA, INC., Plaintiff and Counter-	)	
Defendants.	)	

## **JOINT CLAIM CONSTRUCTION BRIEF FOR THE NS PATENTS**

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## TABLE OF ABBREVIATIONS

Abbreviation	Description
'361 patent	U.S. Patent No. 9,708,361 (Ex. 1)
'322 patent	U.S. Patent No. 10,683,322 (Ex. 2)
Br.	Joint Claim Construction Brief for the NS Patents
Ex. _____	Exhibit Number _____
<i>Italic</i>	Emphasis added unless indicated otherwise
Luedtke Decl.	Declaration of Nathan W. Luedtke, Ph.D. dated February 27, 2023 (Ex. 15)
NS	Plaintiffs/Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc.
Pentelute Decl.	Declaration of Bradley L. Pentelute, Ph.D. dated February 5, 2023 (Ex. 14)
Pentelute Rep. Decl.	Reply Declaration of Bradley L. Pentelute, Ph.D. dated March 13, 2023 (Ex. 20)
Sarepta	Defendant/Counter-Plaintiff Sarepta Therapeutics, Inc.

## EXHIBITS

Exhibit Number	Description
1	U.S. Patent No. 9,708,361
2	U.S. Patent No. 10,683,322
3	Prosecution History Excerpt of U.S. Patent No. 9,708,361
4	Alberts et al., <i>Molecular Biology of the Cell</i> 191-234, 299-374 (4th ed. 2002) (“Alberts 2002”)
5	Chan et al., “Antisense Oligonucleotides: From Design to Therapeutic Application,” <i>Clin. Exp. Pharmacol. Physiol.</i> (2006) 33(5-6): 533-540 (“Chan 2006”)
6	Moulton et al., “Gene Knockdowns in Adult Animals: PPMOs and Vivo-Morpholinos,” <i>Molecules</i> (2009) 14(3): 1304-1323 (“Moulton 2009”)
7	Pon, “Solid-Phase Supports for Oligonucleotide Synthesis,” <i>Curr. Protoc. Nucleic Acid Chem.</i> (2000) 00(1): 3.1.1.-3.1.28 (“Pon 2000”)
8	Summerton et al., “Morpholino Antisense Oligomers: Design, Preparation, and Properties,” <i>Antisense Nucleic Acid Drug Dev.</i> (1997) 7(3): 187-195 (“Summerton 1997”)
9	Summerton, “Morpholinos and PNAs Compared,” <i>Lett. Pept. Sci.</i> (2003) 10: 215-236 (“Summerton 2003”)
10	Collins English Dictionary, 11th ed. (2011)
11	Vyondys 53® (Golodirsen) Prescribing Information (Revised: 2/2021)
12	Ltr. from Mr. Miller dated Jan. 1, 2023
13	Comprehensive Organic Synthesis, 2nd ed. (2014) Vol. 2, pp. 273-339
14	Declaration of Bradley L. Pentelute Ph.D. dated February 5, 2023
15	Declaration of Nathan W. Luedtke, Ph.D. dated February 27, 2023
16	Flickinger et al., “Spatial Photorelease of Oligonucleotides, Using a Safety-Catch Photolabile Linker” <i>Organic Letters</i> , Vol. 8, No. 11 2357-2360 (2006)
17	Weichelt, F., “Topic: Safety-Catch Linker (SCAL)
18	Ti et al., “Transient Protection: Efficient One-Flask Syntheses of Protected Deoxynucleosides,” <i>J. Am. Chem. Soc.</i> , 104, 1316-1319 (1982)
19	MacCoss, et al., “Facile detriylation of nucleoside derivatives by using trifluoracetic acid”
20	Reply Declaration of Dr. Bradley L. Pentelute
21	U.S. Patent No. 10,385,092
22	U.S. Patent No. 10,407,461
23	U.S. Patent No. 10,487,106
24	U.S. Patent No. 10,647,741
25	U.S. Patent No. 10,662,217

## I. INTRODUCTION

### A. NS's Opening Introduction

Pursuant to Paragraph 9 of the Scheduling Order (D.I. 143), Plaintiff/Counter-Defendant Nippon Shinyaku Co. Ltd. and Counter-Defendant NS Pharma, Inc. (collectively “NS”) provide their Opening Brief in support of their proposed claim construction positions for the disputed terms of U.S. Patent Nos. 9,708,361 (“the ’361 Patent,” Ex. 1<sup>1</sup>); 10,385,092 (“the ’092 Patent,” Ex. 21); 10,407,461 (“the ’461 Patent,” Ex. 22); 10,487,106 (“the ’106 Patent,” Ex. 23); 10,647,741 (“the ’741 Patent, Ex. 24); 10,662,217 (“the ’217 Patent, Ex. 25); and 10,683,322 (“the ’322 Patent,” Ex. 2) (collectively, the “NS Patents”).

In its claim construction exchanges, Defendant and Counter-Plaintiff Sarepta Therapeutics, Inc. (“Sarepta”) identified three disputed terms in the NS Patents that it contends need construction: one in the ’361 Patent and two terms in the ’322 Patent. Both parties agree that the terms should be given their plain and ordinary meaning. Sarepta incorrectly alleges that its proposed constructions reflect the “plain and ordinary meaning,” while it actually seeks to re-write the claims in a manner unsupported by the law, namely to (i) include additional and unnecessary negative limitations, (ii) limit the inclusion of additional non-claimed elements, despite the claims use of broad “comprising” language, and (iii) import a specific order to the steps of method claims despite the fact that no such order is required. NS’s proposals, on the other hand, accurately reflect the plain and ordinary meaning of the disputed terms and should be adopted.

### B. Sarepta’s Answering Introduction

Claim construction “begins with the words of the claim.” *Wi-Lan, Inc. v. Apple, Inc.*, 811 F.3d 455, 462 (Fed. Cir. 2016) (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-15 (Fed. Cir.

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<sup>1</sup> Unless otherwise noted, all exhibits referenced herein are attached to the parties’ Joint Appendix to Claim Construction Brief for NS Patents, filed herewith.

2005) (en banc)). Sarepta’s proposed constructions of the three disputed terms from NS’s patents follow this bedrock principle. Sarepta’s construction of “antisense oligomer . . . *consisting of* the nucleotide sequence of SEQ ID NO: 57” gives effect to the closed claim language by specifying both what the antisense oligomer must include (the nucleobase sequence of SEQ ID NO: 57) and exclude (any nucleobase additions, substitutions, or modifications to SEQ ID NO: 57). *See Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358-59 (Fed. Cir. 2016) (holding that “consisting of” is a patent law term of art excluding unrecited elements, steps, or ingredients). Extensive “consisting of” case law supports Sarepta’s construction.

Similarly, Sarepta’s proposed constructions of the ’322 patent claims clarify that the claimed synthesis method requires (1) performing the steps in the specified order and (2) *direct* chemical reactions. The steps of the claimed methods repeatedly refer back to “said Compound” from the previously completed step, mandating that those steps are performed in order. And the steps involve reacting a compound from the prior step with the recited chemical (for example, a deprotecting agent) to form a new compound, i.e., a *direct* chemical reaction. In this respect, the claim language could hardly be clearer that the steps of the method must be performed in the order specified. Consistent with the claim language, the specification only describes a single synthesis method that uses the identical order of steps recited in the claims with no suggestion that the order could be varied in any way.

NS’s proposed constructions, on the other hand, fail to clarify the scope of the claims and deviate from the claim language. Regarding the “consisting of” term, NS’s proposed construction inappropriately leaves open the possibility that the claimed antisense oligomer may include nucleobase additions, substitutions, and modifications. Regarding the ’322 patent claims, NS’s position that the claimed synthesis method does not require a particular sequence of steps is

contrary to the express claim language, which links each step to the preceding step. NS's constructions also conflict with the plain claim language by allowing the claimed synthesis method to include intermediate steps and indirect reactions.

### C. NS's Reply Introduction

Sarepta argues that it's claim construction positions give effect to the words of the claim. They do not. Instead, Sarepta adds (i) unnecessary claim language that will confuse any later performed infringement analysis and (ii) improper limitations restricting the use of additional steps and reagents in a method claim that uses broad "comprising" language. When evaluated in view of relevant legal precedent and evidence, NS's proposed constructions must be adopted and Sarepta's proposed constructions must be rejected.

First, there is no dispute over the literal scope of the claim term "antisense oligomer...consisting of the nucleotide sequence of SEQ ID NO: 57." Both parties acknowledge that the bases in the antisense oligomer must be exactly "guugccuccg guucugaagg uguuc" (i.e., SEQ ID NO: 57). NS's proposed construction aligns with that language by affirmatively describing the required nucleotide bases of the antisense oligomer. Sarepta, on the other hand, adds unnecessary and redundant negative language: "with no nucleobase additions, substitutions, or modifications."

Under either construction, the *literal* infringement analysis is straightforward—either the accused product has the specific nucleotide sequence or it does not. However, Sarepta's proposal—adding unnecessary negative limitations—may confuse a factfinder that must conduct an infringement analysis under the doctrine of equivalents. Specifically, the use of Sarepta's construction may result in a jury questioning (i) whether an otherwise equivalent nucleotide sequence infringes under the doctrine of equivalents, or (ii) whether the equivalents analysis fails under the all-elements rule because Sarepta's negative claim limitations were vitiated. Since

Sarepta’s negative limitations are unnecessary and may cause confusion later in the case, Sarepta’s proposed construction should be rejected and NS’s proposed construction should be adopted.

Second, Sarepta seeks to impose a specific claim order to certain claim limitations found in the ’322 Patent, even though the claims use broad “comprising” language. Sarepta’s construction imports limitations from the specification into the claims and should be rejected. Sarepta argues that the use of “said Compound” in the claims necessitates that the reagent in the next step be the actual product from the previous step—requiring that the claimed steps be performed in order with no additional intermediate steps. Sarepta is wrong. The reference to “said Compound” simply acknowledges that the reagent has been previously defined and has a specific chemical structure that is described in the claim. A POSA would understand that additional unrecited steps could be performed, causing a change in the ultimate order of steps. Accordingly, Sarepta’s proposed construction should be rejected, and NS’s proposed construction, which does not import limitations into the claim, should be adopted.

#### **D. Sarepta’s Sur-Reply Introduction**

NS’s reply highlights the deficiencies in its constructions. For the ’361 patent, NS contends that its construction covers the same scope as Sarepta’s construction. NS’s construction, however, is ambiguous and risks confusing the jury whereas Sarepta’s construction is crystal-clear by explaining what the claims include and exclude. For the ’322 patent, NS seeks to broaden the claims by allowing *each* step to be performed in *any* order using compounds obtained by undisclosed, indirect steps. This violates the stepwise logic of the synthesis scheme, the claims’ plain language, the specification’s teachings, and even NS’s expert’s testimony that most steps must be performed in the listed order.

## II. THE NS PATENTS

### A. NS's Opening Position

The seven NS Patents issued between July 18, 2017 and June 16, 2020 to Nippon Shinyaku Co. Ltd. and the National Center of Neurology and Psychiatry (“NCNP”) as assignees, with named inventors Naoki Watanabe, Youhei Satou, Shin’ichi Takeda, and Tetsuya Nagata. *See* Exs. 1, 2, and 21-25. The NS Patents generally relate to gene therapies used to treat Duchenne Muscular Dystrophy (“DMD”)—a neuromuscular disorder that causes progressive muscle weakness in young boys. The NS Patents treat DMD using oligomers—short genetic sequences—to induce skipping in exon 53 of the human dystrophin gene. *Id.* Certain asserted claims of the NS Patents, including claims 1 and 3-7 of the ’361 Patent, claims 1-3 of the ’092 Patent, claims 1-2 of the ’461 Patent, and claims 1-2 of the ’106 Patent, are directed to a composition of matter—oligomers or subclasses thereof. Exs. 1, 2, and 21-22. Other asserted claims, including claims 1-12 of the ’741 Patent and claims 1-4 of the ’217 Patent are directed to a method of using oligomers or related products to treat DMD. Exs. 23-24. Still other asserted claims, specifically claims 1-10 of the ’322 Patent, are directed towards methods of making oligomers or related compounds. Ex. 25. Regardless of the specific type of claim, each NS Patent generally relates to the same subject matter and share substantially identical specifications. *See* Exs. 1, 2, and 21-25.

In the ’361 Patent, Sarepta identified the term “antisense oligomer . . . consisting of the nucleotide sequence of SEQ ID NO: 57” as requiring construction during the initial claim construction exchanges. This term is found in the only independent claim of the ’361 Patent:

An **antisense oligomer** which causes skipping of the 53rd exon in the human dystrophin gene **consisting of the nucleotide sequence of SEQ ID NO: 57** wherein the antisense oligomer is an oligonucleotide in which the sugar moiety and/or the phosphate-binding region of at least one nucleotide constituting the oligonucleotide is modified, or a morpholino oligomer.

Ex. 1 at claim 1 (emphasis added).

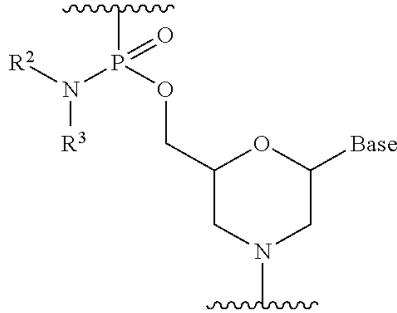
Sarepta has also identified two terms from the '322 Patent (shown below in bold) as requiring construction. The '322 Patent has two independent claims—claims 1 and 6—each directed to a solid phase method of making an oligomer:

1. A solid-phase method of making an oligomer comprising a phosphorodiamidate morpholino oligomer (PMO) and a group at the 5' end of said PMO, wherein said PMO is 100% complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in a human dystrophin pre-mRNA,

wherein the 53rd exon in said human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1,

wherein said PMO hybridizes to said human dystrophin pre-mRNA with Watson-Crick base pairing,

wherein the phosphorodiamidate morpholino monomers of said PMO have the formula:



wherein each of R2 and R3 represents a methyl; and

wherein Base is a nucleobase selected from the group consisting of: uracil, cytosine, thymine, adenine, and guanine; and

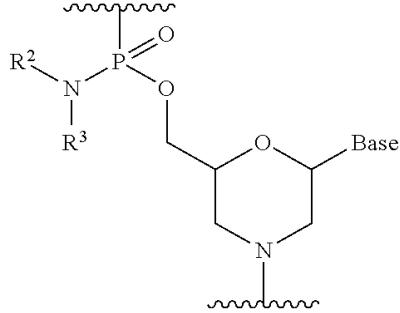
wherein the group at the 5' end of said PMO has the formula:

6. A solid-phase method of making a phosphorodiamidate morpholino oligomer (PMO) that is 100% complementary to the 36th to the 60th nucleotides from the 5' end of the 53rd exon in a human dystrophin pre-mRNA,

wherein the 53rd exon in said human dystrophin pre-mRNA consists of a nucleotide sequence corresponding to SEQ ID NO: 1,

wherein said PMO hybridizes to said human dystrophin pre-mRNA with Watson-Crick base pairing,

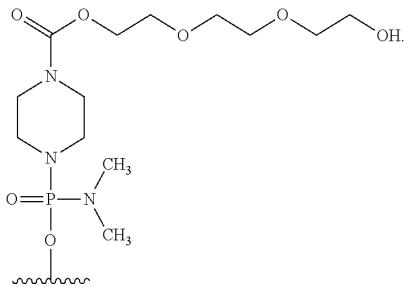
wherein the phosphorodiamidate morpholino monomers of said PMO have the formula:



wherein each of R2 and R3 represents a methyl; and

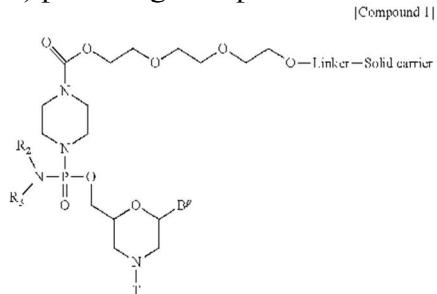
wherein Base is a nucleobase selected from the group consisting of: uracil, cytosine, thymine, adenine, and guanine; and

wherein the 5' end of said PMO has the formula:



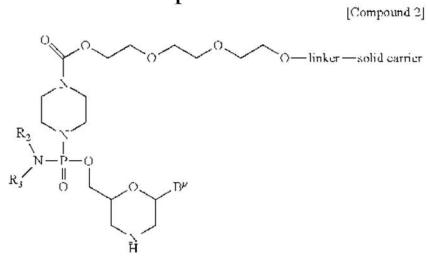
said method comprising:

a) providing Compound 1:



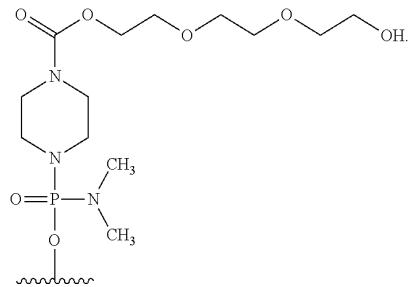
wherein T represents trityl, monomethoxytrityl, or dimethoxytrityl; wherein each of R2 and R3 represents a methyl; and wherein BP is a protected Base,

b) reacting said Compound 1 with an acid to form Compound 2:



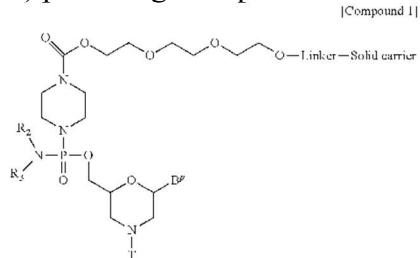
c) reacting said Compound 2 with a morpholino monomer in the presence of a base and a solvent;

d) repeating steps b) and c) until Compound 3 is complete:



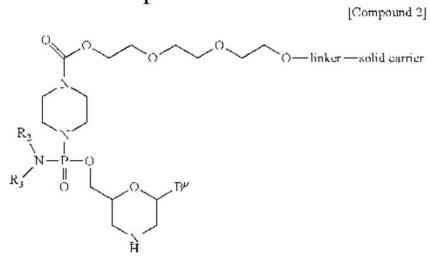
said method comprising:

a) providing Compound 1:



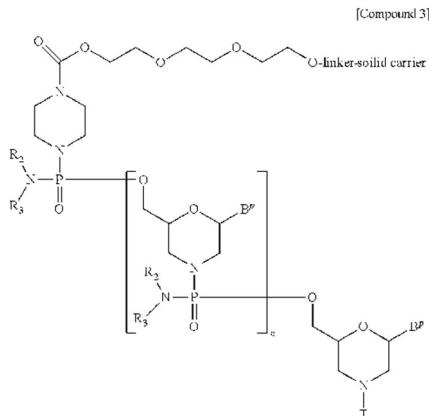
wherein T represents trityl, monomethoxytrityl, or dimethoxytrityl; wherein each of R2 and R3 represents a methyl; and wherein BP is a protected Base,

b) reacting said Compound 1 with an acid to form Compound 2:

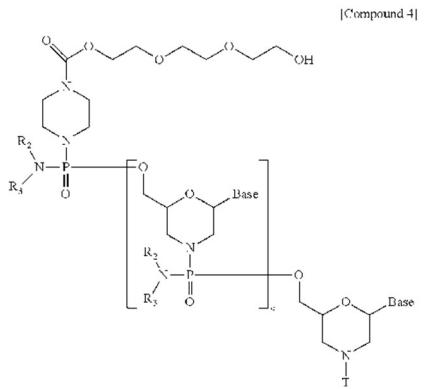


c) reacting said Compound 2 with a morpholino monomer in the presence of a base and a solvent;

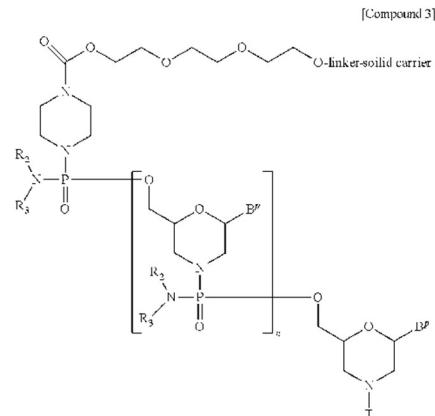
d) repeating steps b) and c) until Compound 3 is complete:



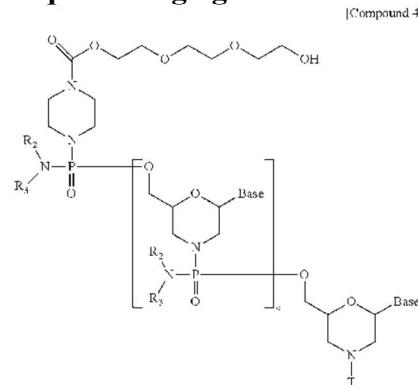
**e) reacting said Compound 3 with a deprotecting agent to form Compound 4:**



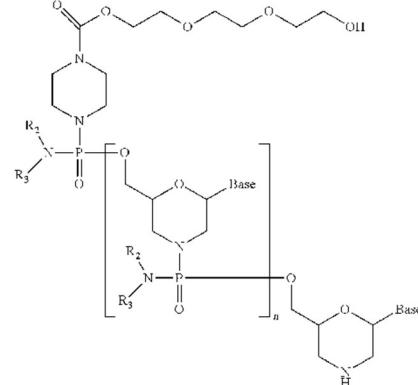
**f) reacting Compound 4 with an acid to form said oligomer.**



**e) reacting said Compound 3 with a deprotecting agent to form Compound 4:**



**f) reacting said Compound 4 with an acid to form said PMO:**



Ex. 2 at claims 1 and 6 (emphasis added). In general, the solid phase method of making an oligomer requires sequentially adding protected nucleotide bases onto a growing oligomer attached to a solid carrier. *Id.* at steps a-d. After the entire oligomer of the desired sequence has been

created and the bulk of the method has been completed, steps e) and f) of the claim involve *simple finishing steps*: deprotecting the last base, removing the last trityl group, and cleaving the oligomer from the solid carrier. *Id.* at steps e-f. It is these last, finishing steps e) and f) that Sarepta claims require construction.

Sarepta has only identified these three terms of the NS Patents as requiring construction—apparently agreeing with NS's position that all remaining terms in the NS Patents should be accorded their plain and ordinary meanings. As set forth below, the three terms of the NS Patents identified by Sarepta should also be given their plain and ordinary meanings, as set forth in NS's proposed constructions.

### **III. DEFINITION OF A SKILLED ARTISAN**

#### **A. Sarepta's Answering Position**

Sarepta proposes that a skilled artisan would have had a Ph.D. in chemistry, biochemistry, cell biology, genetics, molecular biology, or an equivalent, and several years of experience with antisense oligonucleotides for inducing exon skipping. Pentelute Decl. ¶¶21-22; *Phillips*, 415 F.3d at 1312-13 (the “ordinary and customary meaning” is the meaning to a skilled artisan at the time of the invention). NS fails to address the qualifications or experience of a skilled artisan.

To assist the Court's understanding of the disputed synthesis terms from the '322 patent, Sarepta submits the declaration of Bradley L. Pentelute, Ph.D. Pentelute Decl. ¶¶1-12, 16-17. Dr. Pentelute is a Professor of Chemistry at the Massachusetts Institute of Technology (MIT). He also holds positions at the Koch Institute for Integrative Cancer Research at MIT and Broad Institute of MIT and Harvard University, and is a member of the Center for Environmental Health Sciences at MIT. Dr. Pentelute has published more than 100 articles, many of which explore various synthesis methods for making oligonucleotides. He is an inventor of several patents and has founded several companies relating to therapeutics.

**B. NS's Reply Position**

NS disputes the definition of a POSA identified by Sarepta. Sarepta proposes a single definition of a POSA for both the '361 Patent and the '322 Patent: a person having “a Ph.D. in chemistry, biochemistry, cell biology, genetics, molecular biology, or an equivalent, and several years of experience with antisense oligonucleotides for inducing exon skipping.” Br. at 9.

However, the claims of the '361 Patent are directed to antisense oligomers which cause “skipping of the 53<sup>rd</sup> exon in the human dystrophin gene” or “pharmaceutical composition[s] for the treatment of muscular dystrophy” containing those antisense oligomers. Ex. 1, '361 Patent, cls. 1, 7. Accordingly, NS proposes that a “POSA” in the '361 Patent would have had an M.D., Ph.D. or lower degree with expertise in molecular biology, biochemistry or a related area, and experience with neuromuscular or genetic diseases and/or designing and testing antisense oligonucleotides for splice-site switching/exon skipping applications. Sarepta’s proposed POSA for the '361 Patent would exclude those with relevant experience having degrees such as an M.S., B.S./B.A., or M.D. (which makes little sense considering the '361 Patent specifically references pharmaceutical compositions).

On the other hand, the claims of the '322 Patent are directed to a “solid phase method of making” an oligomer. Ex. 2, '322 Patent, cl. 1. Accordingly, NS proposes that a POSA in the '322 Patent would have had a Ph.D. or lower degree in chemistry, biochemistry, cell biology, genetics, molecular biology, or an equivalent, and several years of experience in the synthesis of oligomers, with additional education requiring less experience and vice versa. As Dr. Nathan W. Luedtke, Ph.D., Professor of Chemistry at McGill University, explains, Sarepta’s proposed definition would exclude those with relevant experience having degrees such as an M.S., B.S./B.A., even though such individuals would qualify as a POSA. Ex. 15 ¶¶19-23.

### C. Sarepta's Sur-Reply Position

For the '361 patent, Sarepta agrees that a medical doctor could qualify as a skilled artisan if she had several years of experience designing and using exon skipping antisense oligomers and related therapies. For the '361 and '322 patents, an individual with only an M.S. or B.S./B.A. would have insufficient education or training to qualify as a skilled artisan in view of the highly technical subject matter. Pentelute Rep. Decl. ¶¶1-7. Regardless, under either party's definition, Sarepta's constructions conform to the intrinsic evidence and Dr. Pentelute qualifies as a skilled artisan. *Id.*; Pentelute Decl. ¶¶2-11.

## IV. AGREED-UPON CONSTRUCTIONS

The parties have no agreed-upon constructions.

## V. DISPUTED CONSTRUCTIONS

### A. Term 1: "antisense oligomer . . . consisting of the nucleotide sequence of SEQ ID NO: 57"

<u>Term</u>	<u>NS's Position</u>	<u>Sarepta's Position</u>
<b>"antisense oligomer . . . consisting of the nucleotide sequence of SEQ ID NO: 57"</b> ('361 Patent Claim 1)	Plain and ordinary meaning – i.e., Antisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc)	Antisense oligomer having the sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc) with no nucleobase additions, substitutions or modifications thereof.

### 1. NS's Opening Position

Federal Circuit law imposes a "**heavy presumption . . . biasing** claim construction in favor of the" plain and ordinary meaning. *Home Diagnostics, Inc. v. LifeScan, Inc.*, 381 F.3d 1352, 1355, 1357 (Fed. Cir. 2004) (emphasis added). NS's proposed construction affirmatively identifies the plain and ordinary meaning of the term "antisense oligomer . . . consisting of the nucleotide sequence of SEQ ID NO: 57."

Of key importance is the disputed term’s use of the term “consisting of.” “‘Consisting of’ is a term of patent convention meaning that the claimed invention contains *only what is expressly set forth* in the claim.” *Multilayer*, 831 F.3d at 1358 (quoting *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331 (Fed. Cir. 2004)). Here, the claim expressly sets forth that the antisense oligomer’s nucleotide sequence is the *nucleotide sequence of SEQ ID NO: 57*. Ex. 1 at claim 1. As the ’361 Patent describes, SEQ ID NO: 57 has the nucleotide sequence “guugccuccg guucugaagg uguuc.” *Id.* at Col. 65. Thus, the plain and ordinary meaning of the term shows that the antisense oligomer has a nucleotide sequence that is reflected in SEQ ID NO: 57.

NS’s proposed construction sets forth the plain and ordinary meaning of the disputed term using, like the claim itself, affirmative limitations—i.e., describing what the claim includes: “antisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc).” Because NS’s proposed construction affirmatively sets forth the plain and ordinary meaning of the phrase, it should be adopted. *Home Diagnostics*, 381 F.3d at 1355, 1357.

Sarepta’s construction, on the other hand, should be rejected. First, Sarepta’s proposed construction inappropriately replaces the claim’s use of “consisting of” with the transitional word “having.” Unlike “consisting of,” which is a closed transitional phrase with a well-known meaning, “[t]he transition ‘having’ can . . . make a claim open,” similar to the transitional phrase “comprising.” *Crystal Semiconductor Corp. v. Tritech Microelectronics Int’l, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir. 2001). Accordingly, the first part of Sarepta’s proposed construction—“antisense oligomer having the sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc)”—conflicts with the plain and ordinary meaning of this term. Indeed, because Sarepta has used the open

transition “having,” this portion of the construction is broader than the claim term “antisense oligomer . . . consisting of the nucleotide sequence of SEQ ID NO: 57.”

Sarepta then tries to resolve this problem (of its own making) by adding new negative limitations: “with no nucleobase additions, substitutions or modifications thereof.” But the Federal Circuit has warned against the improper use of negative limitations during claim construction. *Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003) (“[T]here is no basis in the patent specification for adding the negative limitation.”). Given this admonition, district courts have found “that negative limitations, which define an invention in terms of what it does not do rather than what it does, are generally disfavored.” *Precision Energy Servs. v. Thrubit, LLC*, No. H-11-4492, 2013 U.S. Dist. LEXIS 37306, at \*10-11 (S.D. Tex. Mar. 19, 2013) (citing *Omega*, 334 F.3d at 1323); *see also Novartis Pharm. Corp. v. Par Pharm. Inc.*, 2015 U.S. Dist. LEXIS 158443, at \*11 (D. Del. Nov. 23, 2015) (“Negative limitations will generally not be added to claim terms without ‘express disclaimer or independent lexicography in the intrinsic record that justifies including the negative limitation.’” (quoting *Vehicle IP, LLC v. AT & T Mobility, LLC*, 594 F. App’x 636, 642 (Fed. Cir. 2014))).

The Federal Circuit has likewise warned against construing with additional limitations or language when such limitations are not necessary to interpret the plain and ordinary meaning of the disputed term. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1349 (Fed. Cir. 2003) (“Rather than insert an additional limitation into the claim, the better course is to rely on a construction . . . that does not require such an interpolation.”).

Sarepta’s proposed construction runs afoul of this principle as well and should be rejected. It improperly adds negative limitations where such limitations are not separately supported by the specification and are unnecessary. The specification of the ’361 Patent cannot justify these

negative limitations, as it contemplates the use of various bases in its antisense oligomers—including modified bases—not just the four bases that are included in SEQ ID NO: 57. Ex. 1 at 11:36-54 (“The nucleobase includes, for example, adenine, guanine, hypoxanthine, cytosine, thymine, uracil, and modified bases thereof . . .”). The specification also contemplates that useful oligomers may have nucleotide sequences that are adjusted by one to three nucleobases so that they contain specific nucleobases that are “non-complementary to the target nucleotide sequence.” *Id.* at 7:3-20. In short, nothing in the specification or prosecution history of the ’361 Patent suggests that sequences with “nucleobase additions, substitutions or modifications” of SEQ ID NO: 57 has been disavowed or disclaimed. *Novartis Pharm.*, 2015 U.S. Dist. LEXIS 158443 at \*11. To the contrary, the specification acknowledges such nucleobase additions, substitutions and modifications.

Moreover, the additional negative limitation “with no nucleobase additions, substitutions or modifications thereof” is not necessary to explain the plain and ordinary meaning of the disputed phrase—NS’s proposed construction does so without any negative limitations by explaining that phrase means an “antisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc).” Sarepta’s construction includes this additional negative limitation because its affirmative description of the claim term is not specific enough (e.g., it uses open “having” language instead of a more precise affirmative definition). Since Sarepta’s negative limitation is unnecessary, it should not be included in the Court’s construction. *Precision Energy*, No. H-11-4492, 2013 U.S. Dist. LEXIS 37306 at \*10-11 (“[N]egative limitations, which define an invention in terms of what it does not do rather than what it does, are generally disfavored.”) (citing *Omega*, 334 F.3d at 1323); *Boehringer Ingelheim*, 320

F.3d at 1349 (“Rather than insert an additional limitation into the claim, the better course is to rely on a construction . . . that does not require such an interpolation.”).

Since NS’s proposed construction gives the disputed phrase its plain and ordinary meaning using affirmative language and Sarepta’s proposed construction includes additional unnecessary and redundant negative limitations contrary to general claim construction principles, NS’s proposed construction should be adopted and Sarepta’s proposed construction should be rejected.

## **2. Sarepta’s Answering Position**

### **a. Sarepta’s Construction Provides the Meaning of the Disputed Term in Plain Language**

The claim term “consisting of” is “a term of art in patent law” signifying that the “claim element is ‘closed’ and therefore ‘*excludes* any elements, steps, or ingredients not specified in the claim.’” *Multilayer*, 831 F.3d at 1358-59 (citation omitted); *see* Br. at 12.

Sarepta’s construction applies this term of art to the claims using plain language, i.e., explaining that the claimed antisense oligomer has the sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc) with no nucleobase additions, substitutions, or modifications. This construction benefits the factfinder by explaining both what must be included in the claimed antisense oligomer (the nucleobase sequence of SEQ ID NO: 57) and excluded (nucleobase additions, substitutions, and/or modifications to SEQ ID NO: 57). Many courts have adopted, and the Federal Circuit has affirmed, constructions of “consisting of” expressly reciting both what the claim includes and excludes. *See, e.g., Multilayer*, 831 F.3d at 1355, 1358-61 (affirming construction of a claim term “consisting of” certain resins as having the listed resins and “no other resin(s)’’); *Norian*, 363 F.3d at 1331-32 (stating that a kit “consisting of” specified chemicals had those chemicals and “no other chemicals’’); *Otsuka Pharms. Co. v. Lupin Ltd.*, C.A. No. 21-900-RGA, 2022 WL 2952759, at \*3-5 (D. Del. July 26, 2022) (construing composites “consisting of”

two chemicals as composites having those chemicals and “no additional excipients”); *Unimed Pharm., LLC v. Perrigo Co.*, C.A. No. 13-236-RGA, 2015 WL 1094601, at \*5-6 (D. Del. Mar. 11, 2015) (construing “hydroalcoholic gel consisting of” listed ingredients as “a gel employing water and alcohol made from the designated ingredients and *excluding* any element, step or ingredient not designated in the claim”).<sup>2</sup>

The prosecution history of the ’361 patent supports Sarepta’s construction. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (the prosecution history can be helpful “to ascertain the true meaning of language used in the patent claims”). As initially pursued, the claims encompassed antisense oligonucleotides with the base sequence of SEQ ID NO: 57 (containing A, U, G, and C bases only) *as well as* other antisense oligonucleotides with substituted or modified nucleotides (for example, T) that were “complementary to . . . the 36th to the 60th” nucleotides of “the 53rd exon in the human dystrophin gene.” Ex. 3 at NS00000602. In response to an obviousness rejection, the applicants amended the claims to limit them to antisense oligonucleotides “consisting of the nucleotide sequence of . . . SEQ ID NO: 57.” *Id.* at NS00000756, -759-761. The applicants’ narrowing amendment, which ultimately led to the allowance of the ’361 patent (*id.* at NS00000803-808), confirms that the disputed phrase excludes nucleobase additions, substitutions, or modifications.

**b. NS’s Criticisms of Sarepta’s Construction Are Misguided**

NS appears to acknowledge that, in view of the closed “consisting of” claim language, the nucleotide sequence of the claimed antisense oligomers must be identical to that set forth in SEQ ID NO: 57 (guugccuccg guucugaagg uguuc) with no nucleobase additions, substitutions, or modifications. *See* Br. 9; Ex. 12 (Ltr. from Mr. Miller dated Jan. 1, 2023). But NS objects to

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<sup>2</sup> Sarepta’s Vyondys 53® (golodirsen) product does *not* have the nucleobase sequence of SEQ ID NO: 57, differing at 9 of 25 positions. Ex. 11 at §11.

Sarepta’s use of the term “having,” alleging that it makes the disputed phrase “broader.” Br. at 12-13. NS then argues that Sarepta attempts to remedy this by adding a purported “negative limitation” that defines the invention by “what it does not do rather than what it does.” *Id.*

NS’s criticisms lack merit. As in the *Multilayer*, *Norian*, *Otsuka*, and *Unimed* cases discussed above, Sarepta’s construction uses plain language to explain the legal term “consisting of,” making clear both what the claimed antisense oligonucleotide includes (“the sequence of SEQ ID NO: 57”) and excludes (“no nucleobase additions, substitutions, or modifications” to SEQ ID NO: 57). Use of the term “having” does not expand the scope of the claim—it clarifies what is included within the claim’s scope. And the “no nucleobase additions, substitutions, or modifications” language is not a negative limitation—it simply explains in plain language what the claim excludes. Collectively, Sarepta’s proposed construction explains what the claim covers, and excludes, using terms familiar to a skilled artisan in accordance with applicable law.

The so-called “negative limitation” cases cited by NS are inapposite. *See* Br. at 13. Importantly, *none* involved construing a “consisting of” claim term. For example, *Omega* involved means-plus-function claim language, not “consisting of” claim language. The Federal Circuit held that the district court erred in adding a negative limitation that had “no support in the text of the claims.” 334 F.3d at 1322-23. Similarly, *Novartis Pharmaceuticals Corp. v. Par Pharmaceutical, Inc.* did not involve “consisting of” claim language. The district court found no support for the plaintiffs’ proposed construction (which included a negative limitation) but then adopted the defendants’ proposed construction that *included* a different negative limitation. C.A. No. 14-1494-RGA, 2015 WL 7566615, at \*2-4 (D. Del. Nov. 23, 2015) (construing “solid mixture” as a solid combination of two or more solid substances that are mixed “but *not* chemically combined”). In short, NS’s cited cases are not contrary to Sarepta’s position that the closed

“consisting of” claim language here excludes nucleobase additions, substitutions, or modifications. *See Multilayer*, 831 F.3d at 1358-59.

Similarly, NS’s assertion that Sarepta’s construction inserts an “additional limitation” into the claim is wrong. *See* Br. at 13 (citing *Boehringer*, 320 F.3d at 1349). In *Boehringer*, the “additional limitation” *changed the scope of the claim* by inappropriately defining the ending point for an incubation period with a quantifier that was unsupported by the claim language. 320 F.3d at 1349. Here, Sarepta’s proposed inclusion of the phrase “with no nucleobase additions, substitutions or modifications thereof” does not add a limitation or change the claim scope. Instead, it clarifies precisely what the claim covers based on the limitation “consisting of.” NS does not argue otherwise, asserting only that the language is purportedly “redundant.” Br. at 15.

Further, NS offers contradictory positions on whether the claim language is open or closed. NS acknowledges on the one hand that the claim term “consisting of” means “that the claimed invention contains *only what is expressly set forth* in the claim.” Br. at 12 (emphasis in original). But NS then argues that the specification “*contemplates the use of various bases in its antisense oligomers—including modified bases—not just the four bases that are included in SEQ ID NO: 57.*” Br. at 14. Thus, while giving lip service to the closed claim language, NS’s proposed construction is plainly intended to allow NS to argue at trial that the claims are *not* closed. Regardless of what the specification discloses, however, NS’s decision to use “consisting of” claim language necessarily *excludes* nucleobase additions, substitutions, or modifications of SEQ ID NO: 57 as a matter of law. *See Multilayer*, 831 F.3d at 1359-60 (listing additional embodiments in the specification fails to overcome the presumption of closed claim language created by “consisting of” claim language); *see also General Elec. Co. v. Int’l Trade Comm’n*, 685 F.3d 1034, 1041 (Fed. Cir. 2012) (“[A] possibly broader disclosure accompanied by an explicit narrow claim

shows the inventor’s selection of the narrow claim scope.”). NS’s self-contradictory arguments highlight why Sarepta’s construction should be adopted to avoid potential jury confusion at trial.

**c. Sarepta’s Construction Provides the Meaning of the Disputed Term in Plain Language**

NS proposes that the claim term should be given its plain and ordinary meaning, which NS asserts is an “antisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc).” This proposed construction, however, fails at the most fundamental level because it does not help the factfinder ascertain the proper scope of the claims. *Phillips*, 415 F.3d at 1312-14.

The claim term “consisting of” carries a specific legal meaning. *See Multilayer*, 831 F.3d at 1358-59. NS cites *no evidence*, either intrinsic or extrinsic, illustrating how its construction purportedly conforms to a skilled artisan’s understanding of this legal term. *See* Br. at 11; *Phillips*, 415 F.3d at 1314 (“[D]etermining the ordinary and customary meaning of a claim requires examination of terms that have a particular meaning *in a field of art.*”); *see supra* § III.A. Unsupported arguments from NS’s attorneys cannot establish the plain and ordinary meaning of the claims. *Va. Innovation Scis., Inc. v. Samsung Elecs. Co.*, 614 F. App’x 503, 511 (Fed. Cir. 2015) (“attorney arguments are not relevant intrinsic or extrinsic evidence” for claim construction).

NS also argues that its construction is preferred because it explains the meaning of the term using “affirmative limitations”—i.e., describing what the claim includes.” Br. at 11-12, 15. But NS’s construction simply converts “*consisting of* the nucleotide sequence” to “is the *specific* nucleotide sequence.” Without further explanation, it is not clear what is covered, or that the claim language excludes nucleobase additions, substitutions, and modifications of SEQ ID NO: 57. Indeed, this potential confusion was reflected in the correspondence between the parties relating to this claim term. Ex. 12 (NS counsel stating: “I believe you misunderstood our position with

respect to the first term. Our position is not that the term of the '361 Patent permits nucleobase additions, substitutions, or modifications.”).

Ultimately, NS’s construction is contrary to the closed “consisting of” claim language and controlling case law on the meaning of that legal term. *See supra* § V.A.2.a. NS’s construction, which does not clarify the boundaries of the disputed term, would not help the factfinder to resolve issues in this case. *See Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1348 (Fed. Cir. 2010) (“The terms, as construed by the court, must ‘ensure that the jury fully understands the court’s claim construction rulings and what the patentee covered by the claims.’”) (citation omitted). In contrast, Sarepta’s proposed construction explains precisely what is covered and not covered and should therefore be adopted.

### **3. NS’s Reply Position**

#### **a. There is No Dispute Between The Parties Regarding Literal Claim Scope**

Sarepta argues that NS’s claim construction must be rejected because it (i) “is plainly intended to allow NS to argue at trial that the claims are *not* closed [i.e., that it is not limited to the specific nucleotide sequence listed]” and (ii) “does not help the factfinder ascertain the proper scope of the claims.” Br. at 18-20. Contrary to Sarepta’s claims, there is no dispute as to the appropriate *literal* claim scope: the claimed antisense oligomer must have the exact bases “guugccuccg guucugaagg uguuc” (i.e., SEQ ID NO: 57). NS’s proposed construction uses clear, affirmative language to describe this limitation: “antisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc).” To fall within claim 1, as construed by NS and Sarepta, the bases of the antisense oligomer must be guugccuccg guucugaagg uguuc. If the bases do not exactly match, then the antisense oligomer is outside the *literal* scope of claim 1. Thus, both proposed constructions

provide the same literal claim scope, and there is no basis to differentiate claim scope on those grounds.

**b. Sarepta’s Proposed Construction Includes Unnecessary Additional Language and Should be Rejected**

As described above, both NS’s and Sarepta’s proposed constructions provide the same literal claim scope. However, the parties took different approaches in proposing their respective constructions. NS’s proposed construction sets forth the plain and ordinary meaning of the disputed term using, like the claim itself, affirmative limitations—*i.e.*, describing what the claim includes: “antisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc).” Sarepta, on the other hand, adds negative limitations: “with no nucleobase additions, substitutions or modifications thereof.” “Negative limitations...define an invention in terms of what it does not do rather than what it does.” *Precision Energy*, 2013 U.S. Dist. LEXIS 37306, at \*10-11 (citing *Omega*, 334 F.3d at 1323).

Sarepta argues that its negative limitations are appropriate and necessary because the claim uses “consisting of,” which “*excludes* any elements, steps, or ingredients not specified in the claim.” Br. at 15-20.

First, Sarepta argues that “[m]any courts have adopted, and the Federal Circuit has affirmed, constructions of ‘consisting of’ expressly reciting both what the claim includes *and* excludes.” *Id.* at 15-16. But Sarepta fails to acknowledge that each case it relies on *involved a dispute* over what the plain language of the claim explicitly “excluded.” In other words, determining what was “excluded” was central to the literal infringement analysis.

For example, in *Multilayer*, 831 F.3d at 1356, the Federal Circuit affirmed a construction “excluding blends of more than one type of resin and all unlisted resins” because it was a central dispute as to whether a blend of resins would fall within the literal scope of the claim. *Id.*; *see also*

*Norian*, 363 F.3d at 1331 (finding that a claim to a kit included specified chemicals and “no other chemicals” but did not exclude an unrecited spatula, in order to determine whether a kit that included a spatula would fall within the literal scope of the claim); *Otsuka Pharm. Co., Ltd. v. Lupin Ltd.*, No. 21-900-RGA, 2022 U.S. Dist. LEXIS 132268, at \*10 (D. Del. July 26, 2022) (adopting a construction that composites contain “no additional excipients” in order to resolve a dispute as to whether the literal scope of the claim allowed for “residual solvents”); *Unimed Pharm., LLC v. Perrigo Co.*, Civil Action No. 13-236-RGA, 2015 U.S. Dist. LEXIS 29703, at \*15 (D. Del. Mar. 11, 2015) (adopting a construction “excluding any element, step or ingredient not designated in the claim” to resolve a dispute as to whether ingredients used in preparing the claimed product but not present in the final composition are included within the literal scope). Here, there is ***no dispute*** as to the literal scope of the claim, rendering Sarepta’s additional “exclusion” language unnecessary. Accordingly, Sarepta’s reliance on *Multilayer*, *Norian*, *Otsuka*, and *Unimed* is unavailing.

Second, since both parties’ constructions provide the same claim scope, NS’s proposed construction—which does not include unnecessary negative limitations—should be adopted. Indeed, Sarepta’s argument that negative limitations can sometimes be appropriate in certain situations does not overcome the precedent finding that such limitations are “disfavored” and that the “better course” is to adopt constructions that do not require such additional language. *Precision*, 2013 U.S. Dist. LEXIS 37306 at \*10-11 (“negative limitations, which define an invention in terms of what it does not do rather than what it does, are generally disfavored”) (citing *Omega*, 334 F.3d at 1323); *Boehringer*, 320 F.3d at 1349 (“Rather than insert an additional limitation into the claim, the better course is to rely on a construction...that does not require such an interpolation.”).

Third, Sarepta’s proposed construction is not commensurate with the “consisting of” language used in the claim. As Sarepta itself notes, the use of “consisting of” “excludes *any* elements, steps, or ingredients ***not specified in the claim.***” Br. at 15 (emphasis added). Sarepta’s proposed construction, on the other hand, only excludes “nucleobase additions, substitutions or modifications.” Under Sarepta’s arguments, in order to give full effect to the “consisting of” language, the parties should recite ***everything*** that must be excluded and anything other than a complete list of what is excluded “fails at the most fundamental level because it does not help the factfinder ascertain the proper scope of the claims.” Br. at 19. Indeed, Sarepta’s construction does not meet its stated goal because it fails to inform the fact finder that antisense oligonucleotides with (i) 50 nucleotide bases, or (ii) nucleotide subtractions, or (iii) certain backbone chemistries are also excluded, among an infinite list of other things. *Id.* at 17 (“Sarepta’s construction uses plain language to explain the legal term “consisting of,” making clear both what the claimed antisense oligonucleotide includes... and excludes.”).

The clear rebuttal to Sarepta’s argument is apparent—it is impossible to list everything that a consisting of claim excludes. Accordingly, unless exclusionary language is needed to resolve an actual dispute between the parties, negative limitations like Sarepta’s should be avoided and Sarepta’s construction should be rejected. *Precision*, 2013 U.S. Dist. LEXIS 37306, at \*10-11 (“negative limitations, which define an invention in terms of what it does not do rather than what it does, are generally disfavored”) (citing *Omega*, 334 F.3d at 1323); *Boehringer*, 320 F.3d at 1349 (“Rather than insert an additional limitation into the claim, the better course is to rely on a construction...that does not require such an interpolation.”).

Fourth, Sarepta’s reliance on the prosecution history of the ’361 Patent is misplaced. Br. at 16. The “consisting of” language was present in the original claims of the ’361 Patent. Ex. 3 at

NS00000602 (showing no amendment of the “consisting of” language). The amendment to the claims has nothing to do with whether the claims are limited to the specific nucleobase sequence of SEQ ID NO. 57. And, more importantly, *NS’s claim scope already limits the literal scope of the claim to the specific nucleobase sequence of SEQ ID NO. 57*—Sarepta’s additional exclusion language is not needed to do so. Accordingly, Sarepta’s arguments related to the prosecution history are simply irrelevant.

Because NS’s proposed construction gives the disputed phrase its plain and ordinary meaning using affirmative language and Sarepta’s proposed construction includes additional unnecessary and redundant negative limitations contrary to general claim construction principles, NS’s proposed construction should be adopted and Sarepta’s proposed construction should be rejected.

**c. Sarepta’s Proposed Construction Will Complicate the Infringement Analysis and Should be Rejected**

As previously discussed, there is no dispute between the parties as to the literal scope of claim 1 of the ’361 Patent. To evaluate literal infringement under either construction, the parties will determine whether the bases of the antisense oligomer are “guugccuccg guucugaagg uguuc.” If the bases are not the same, then the antisense oligomer is outside the *literal* scope of claim 1—regardless of whose proposed construction is adopted. Sarepta’s proposed construction will complicate any analysis of infringement under the doctrine of equivalents because of the additional language “with no nucleobase additions, substitutions or modifications thereof.”

One of the bedrock principles of infringement under the doctrine of equivalents is the “all-elements rule.” “Under the all elements rule, there can be no infringement under the doctrine of equivalents if even one limitation of a claim or its equivalent is not present in the accused device.”

*Lockheed Martin Corp. v. Space Systems/Loral, Inc.*, 324 F.3d 1308, 1321 (Fed. Cir. 2003). In

other words, if “a finding of infringement under the doctrine of equivalents would *entirely vitiate a particular claimed element*, then the court should rule that there is no infringement under the doctrine of equivalents.” *Id.*

Sarepta’s proposed construction will complicate and confuse the analysis under the doctrine of equivalents with respect to this rule. Specifically, under Sarepta’s construction, it is unclear whether the language “with no nucleobase additions, substitutions or modifications thereof” is its own, separate element, or whether it is included as part of a single, larger element: “Antisense oligomer having the sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc) with no nucleobase additions, substitutions or modifications thereof.” Such a question would undoubtedly confuse the factfinder. Moreover, if “with no nucleobase additions, substitutions or modifications thereof” were found to be its own element, that would raise additional questions as to vitiation of that element, *i.e.*, whether a product with an otherwise equivalent nucleobase sequence could be found not to infringe under the doctrine of equivalents due to vitiation of an element that was not present in the original claim language.<sup>3</sup>

NS’s proposed construction avoids this problem and makes it clear that “[a]ntisense oligomer with a nucleotide sequence that is the specific nucleotide sequence of SEQ ID NO: 57 (guugccuccg guucugaagg uguuc)” is a single element for doctrine of equivalents purposes. Since NS’s proposed construction provides a POSA with a clear and unambiguous understanding of the scope of the disputed term and avoids unnecessary language that may cause complications with infringement analysis, NS’s proposed construction should be adopted, and Sarepta’s proposed construction should be rejected.

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<sup>3</sup> Of course, Sarepta may raise other arguments as to why the doctrine of equivalents is inapplicable, but such arguments are not relevant to the issue of claim construction.

#### **4. Sarepta’s Sur-Reply Position**

##### **a. NS’s Construction Is Unclear**

NS asserts that “there is no dispute as to the appropriate literal claim scope,” as the bases must be “exactly” those recited in the claims. Br. at 20-21, 24. But NS’s proposed construction does not make this clear—and is ripe for manipulation. For example, NS continues to assert *literal* infringement even though Sarepta’s product does *not* contain the recited nucleotides. D.I. 86 at ¶97; Br. at 16 n.2. NS also argues that the specification discusses “use of *various* bases,” not just “the four bases that are included in SEQ ID NO: 57.” Br. at 13-14.

In contrast, Sarepta’s construction clarifies the scope of the claims because it identifies both what the claims include (the nucleobase sequence of SEQ ID NO: 57) and exclude (nucleobase additions, substitutions, and/or modifications). Because NS concedes that the claims require “the exact bases” of SEQ ID NO: 57 (Br. at 20-21), it cannot meaningfully dispute Sarepta’s construction.

##### **b. The Doctrine of Equivalents Is Irrelevant**

NS argues that Sarepta’s construction would complicate “analysis of infringement under the doctrine of equivalents,” including “vitiation.” Br. at 24-25. But this is irrelevant to claim construction, as shown by NS’s failure to cite *any* supporting case. *See id.* Indeed, the Federal Circuit has cautioned against addressing questions that “go to infringement” while resolving claim construction disputes. *Eon Corp. IP Holdings v. Silver Spring Networks, Inc.*, 815 F.3d 1314, 1319 (Fed. Cir. 2016); *see Control Res., Inc. v. Delta Elecs., Inc.*, 133 F. Supp. 2d. 121, 126-27 (D. Mass. 2001) (warning against conflating “the legal explication required by *Markman* with the fact-finding role reserved for the jury”).

NS’s assertion that Sarepta’s construction would complicate analyzing “vitiation” is also entirely speculative. Other legal doctrines, including prosecution history estoppel, will preclude

NS from recapturing claim scope that it surrendered during prosecution (i.e., nucleobase modifications). *See Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 734 (2002). Thus, “vitiation” may never be reached, and NS’s speculation is irrelevant.

**c. NS’s Other Criticisms Lack Merit**

NS’s other criticisms of Sarepta’s construction lack merit. Br. at 21-24. *First*, NS argues that Sarepta’s construction adds a “negative limitation,” which “define[s] an invention in terms of what it does not do rather than what it does.” *Id.* at 22, 21 (citing *Precision*, 2013 WL 1155250, at \*4).<sup>4</sup> Not so. Unlike negative functional limitations that lack meaningful structure, Sarepta’s construction defines the claimed oligomer by its chemical structure (requiring a precise base sequence without modifications). It does not define the oligomer functionally by “what it does not do.”

*Second*, NS argues that this case differs from prior “consisting of” cases because claim scope is not disputed. Br. at 21-22. But NS has maintained a literal infringement claim while suggesting that the claims permit base modifications—thus, claim scope *is* disputed. *See supra* § V.A.4.a. Regardless, Sarepta’s construction gives proper legal effect to the term “consisting of” by explaining what it excludes. *E.g., Galderma Lab’ys L.P. v. Teva Pharm. USA, Inc.*, C.A. No. 1:17-cv-01783-RGA, 2018 WL 4290390, at \*12-13 (D. Del. Sept. 7, 2018) (adopting a construction of “consisting of” that excluded unlisted ingredients because it gave “proper legal effect” to the term).

*Third*, NS criticizes Sarepta’s construction for not reciting “*everything* that must be excluded” from the claims. Br. at 23 (emphasis in original). But the disputed term refers to

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<sup>4</sup> Like NS’s other negative limitation cases, *Precision* did not involve construction of the closed transitional term “consisting of.” *Precision*, 2013 WL 1155250, at \*3. Further, the court *adopted* a negative limitation following the patentee’s narrowing amendment, similar to NS’s amendment during prosecution here. *Id.* at \*4-5; Br. at 16.

*nucleotide sequences* (“consisting of the *nucleotide sequence* of SEQ ID NO: 57”). It does not address other portions of the oligomer; neither does Sarepta’s construction. *See Digene Corp. v. Third Wave Techs., Inc.*, 323 F. App’x 902, 909 (Fed. Cir. 2009) (“consisting of” in a clause only limits “those elements found in that particular clause”). NS’s suggestion that “everything” must be addressed by the “consisting of” language—e.g., backbone chemistries *not* in the disputed phrase—is legally erroneous.

*Fourth*, NS argues that the prosecution history of the ’361 patent is irrelevant. Br. at 23-24. But NS ignores the substance of that prosecution history. Br. at 16. While the claims before amendment recited “consisting of,” they encompassed nucleobase modifications of SEQ ID NO: 57. Ex. 3 at NS00000602. In response to a rejection, NS limited the claims to those “consisting of the nucleotide sequence of . . . SEQ ID NO: 57.” *Id.* at NS00000756, -759-761, -788. Sarepta’s proposed construction should be adopted.

**B. Term 2: “e) reacting said Compound 3 with a deprotecting agent to form Compound 4”**

<u>Term</u>	<u>NS’s Position</u>	<u>Sarepta’s Position</u>
“e) reacting said Compound 3 with a deprotecting agent to form Compound 4” (’322 Patent Claims 1 and 6)	Plain and ordinary meaning – i.e., chemically reacting Compound 3 with a deprotecting agent, in order to form Compound 4	Plain and ordinary meaning, i.e., chemically reacting a deprotecting agent directly with Compound 3 of step d), which results in Compound 4.

**1. NS’s Opening Position**

Like with Term 1, NS’s proposal gives the disputed term its plain and ordinary meaning. *Home Diagnostics*, 381 F.3d at 1355, 1357 (noting that Federal Circuit law provides a “heavy presumption . . . biasing claim construction in favor of the” plain and ordinary meaning). Indeed, claim terms “are generally given their ordinary and customary meaning,” i.e., the meaning that

they “would have to a person of ordinary skill in the art in question at the time of the invention.” *Phillips*, 415 F.3d at 1312–13 (citations omitted); *see also Voda v. Cordis Corp.*, 536 F.3d 1311, 1319 (Fed. Cir. 2008).

Here, both parties agree that the plain and ordinary meaning of the term “e) reacting said Compound 3 with a deprotecting agent to form Compound 4” requires “chemically reacting” at least two ingredients—Compound 3 and a deprotecting agent—in order to form a specific result—Compound 4. NS’s proposed construction stops at the plain and ordinary meaning (and should be adopted for that reason). Sarepta’s proposed construction, on the other hand, includes additional limitations that are not found in the plain and ordinary meaning of the disputed term. First, Sarepta includes a requirement that the two ingredients be reacted “directly” together—which a person of ordinary skill in the art would understand to mean without any other reagents or ingredients used as part of the reaction. Second, Sarepta requires that one of the ingredients—Compound 3—be the result of another step of the method claim (step d)). Since neither of Sarepta’s proposed additions is supported by the relevant case law or the intrinsic record, Sarepta’s proposed construction should be rejected.

To understand why Sarepta’s additional limitations must be rejected, it is necessary to recognize that the independent claims in which Term 2 is found use the broad language “comprising” as its transitional phrase. *See Ex. 2 at claims 1 and 6 (using the transition “said method comprising”).* The use of “comprising” creates a presumption that the recited elements are only a part of the [invention], that ***the claim does not exclude additional, unrecited elements.***

*Multilayer Stretch*, 831 F.3d at 1358 (quoting *Crystal Semiconductor*, 246 F.3d at 1348).

This claim construction principle is fatal to Sarepta’s first argument—the improper inclusion of “directly” in its proposed construction. By including the requirement that the disputed

term includes “chemically reacting a deprotecting agent *directly* with Compound 3,” Sarepta improperly excludes “additional, unrecited” reagents or ingredients from the step. The use of “comprising” as the transitional phrase permits such “indirect” reactions. Indeed, the specification of the ’322 Patent identifies additional ingredients as being permissibly used along with the deprotecting agent in the same reaction. Ex. 2 at 22:5-59 (“The ‘deprotecting agent’ used in this step may also be used as a dilution with, e.g., water, methanol, ethanol, isopropyl alcohol, acetonitrile, tetrahydrofuran, DMF, . . .”). Even if Sarepta characterized the only embodiment in the ’322 Patent as reacting the deprotecting agent directly with Compound 3, its argument would still be improper under governing law. *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1308-10 (Fed. Cir. 2014) (“[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment . . .”); *Fiber Optic Designs, Inc. v. Seasonal Specialties, LLC*, 172 F. App’x 995, 997 (Fed. Cir. 2006) (“[T]he standard rule [is] that a claim construction should decline to incorporate additional limitations from the specification.”). Thus, because the plain and ordinary meaning of the disputed term does not require Compound 3 to be reacted “directly” with a deprotecting agent, Sarepta’s proposed construction must be rejected.

The claims’ use of “comprising” is also fatal to Sarepta’s second argument—the improper importation of a step order into the method claims by requiring the use of Compound 3 “of step d.” In general, “[a]bsent affirmative indication to the contrary, method steps need not be performed in the order in which they are recited.” *Cybersettle, Inc. v. Nat’l Arbitration Forum, Inc.*, 243 Fed. Appx. 603 (Fed. Cir. 2007). Sarepta will likely argue that the claim language of the methods steps themselves implicitly require that they be practiced in a specific order. *See* Ex. 2 at claims 1 and 6 (step a) starting with Compound 1; step b) reacting Compound 1 as an ingredient

to form Compound 2; etc.). The claims use the transitional phrase “comprising,” and “[t]he transition ‘comprising’ in a **method claim** indicates that the claim is open-ended and **allows for additional steps.**” *Medichem, S.A. v. Rolabo, S.L.*, 353 F.3d 928, 933 (Fed. Cir. 2003) (quoting *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003)) (emphasis added). “**Since the claim is not foreclosed to additional steps, the steps themselves are not foreclosed from being carried out in a different order than stated in the claim.**” *Lincoln Nat'l Life Ins. Co. v. Transamerica Fin. Life Ins. Co.*, 2007 U.S. Dist. LEXIS 16822, at \*35 (N.D. Ind. Mar. 6, 2007).

Compare, for example, the following two methods—one using only the steps set forth in claims 1 and 6 of the ’322 Patent, and one including additional steps:

Step Number	Method A (Only Claimed Steps)	Method B (Additional Unrecited Steps)
1	Step a) – Providing Compound 1	Step a) – Providing Compound 1
2	Step b) – Forming Compound 2	Step b) – Forming Compound 2
3	Step c) – Reacting Compound 2 with a monomer	Step c) – Reacting Compound 2 with a monomer
4	Step d) – repeating steps b) and c) to form Compound 3	Step d) – repeating steps b) and c) to form Compound 3
5		Reacting Compound 3 with a reagent to form an intermediate.
6		Reacting the intermediate with a second reagent to re-form Compound 3.
7	Step e) – Reacting Compound 3 with reagent to form Compound 4	Step e) – Reacting Compound 3 with reagent to form Compound 4
8	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO

Each of these methods practice all of the steps of claims 1 and 6. However, adding Sarepta’s proposed limitation, that step e) requires using Compound 3 “of step d)” would improperly result in Method B no longer practicing all of the steps—because, in this scenario

Method B uses Compound 3 of an intermediate step (Step 6), not Compound 3 “of step d.” This clearly erroneous result shows why Sarepta’s proposed construction must be rejected.

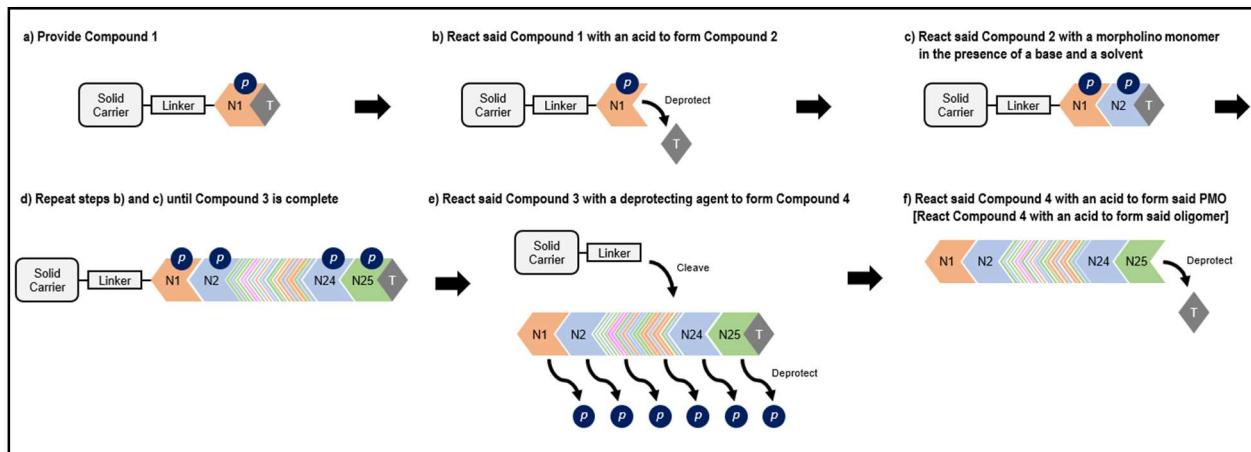
Again, Sarepta may argue that the only embodiments in the specification of the ’322 Patent describe the method steps in the specific order as recited in the claims, with no additional steps. Ex. 2 at 14:1-23:67. But absent disavowal or disclaimer—neither of which are present here—limitations should not be imported from the specification into the claim. *GE Lighting*, 750 F.3d at 1308-10 (“[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment . . . .”); *Fiber Optic*, 172 F. App’x at 997 (“[T]he standard rule [is] that a claim construction should decline to incorporate additional limitations from the specification.”).

Since NS’s proposed construction gives the disputed phrase its plain and ordinary meaning and Sarepta’s proposed construction imports additional limitations contrary to claim construction principles, NS’s proposed construction should be adopted and Sarepta’s proposed construction should be rejected.

## **2. Sarepta’s Answering Position**

Claims 1 and 6 of the ’322 patent are both directed to a solid-phase method of making a PMO via a series of steps, labeled a) through f). Pentelute Decl. ¶¶13-15. As the following schematic shows, the method assembles PMO monomers one-by-one into a growing chain. Pentelute Decl. ¶¶23-39; *see also* Ex. 5 at 533-56; Ex. 6 at 1305-06; Ex. 7 at Fig. 3.1.1; Ex. 8 at Fig. 5B; Ex. 9 at Fig. 4B. In step a), the first PMO monomer is provided attached to a solid carrier via a linker (Compound 1). The PMO monomer contains a protecting group (T), which prevents unwanted chemical reactions. In step b), the attached monomer is deprotected at its 3’-nitrogen position (forming Compound 2) (i.e., the protecting group (T) is removed, permitting reactions at the 3’-end), and then coupled with another monomer in step c). Step d) repeats steps b) and c)

until all of the intended PMO monomers are coupled as a linear chain (Compound 3). Step e) uses a deprotecting agent to deprotect the base of each PMO monomer and to cleave the chain of PMO monomers from the solid carrier (Compound 4). In step f), the final, terminal protecting group is removed using an acid, resulting in the desired PMO.



**Figure 1.** Schematic Representation of NS's Synthesis Methods  
(Pentelute Decl. ¶¶29-39)

As discussed below, Sarepta's construction of step e) requires the steps to be performed in the order written, i.e., Compound 3 produced in step d) is used in step e). Sarepta's construction also reflects the nature of this reaction, i.e., Compound 3 reacts directly with a deprotecting agent to form Compound 4. NS disagrees, alleging that Sarepta's construction incorporating the order of the steps and the nature of the chemical reaction conflicts with the open transitional phrase "comprising." Br. at 28-32. NS is incorrect.

#### **a. The Recited Steps Must Be Performed in the Order Written**

"[A] claim 'requires an ordering of steps when the claim language, as a matter of logic or grammar, requires that the steps be performed in the order written, or the specification directly or implicitly requires' an order of steps." *Mformation Techs., Inc. v. Research in Motion Ltd.*, 764 F.3d 1392, 1398 (Fed. Cir. 2014) (citation omitted). Here, both the claim language and the

specification demonstrate that the claimed synthesis method requires that the recited steps must be carried out in the order specified.

The plain language and structure of the claims are clear. Pentelute Decl. ¶¶40-43. An annotated version of illustrative claim 6 is reproduced below, with the chemical structures of Compounds 1-4 removed:

6. A solid-phase method of making a phosphorodiamidate morpholino oligomer (PMO) . . . said method comprising:

- a) providing Compound 1: . . . ;
- b) reacting said Compound 1 with an acid to form Compound 2;
- c) reacting said Compound 2 with a morpholino monomer in the presence of a base and a solvent;
- d) repeating steps b) and c) until Compound 3 is complete;
- e) reacting said Compound 3 with a deprotecting agent to form Compound 4; and
- f) reacting said Compound 4 with an acid to form said PMO: . . . .

The method begins with step a), in which Compound 1, a solid carrier linked to a morpholino monomer, is provided. Step b) requires reacting “said Compound 1” to form Compound 2. Step c) in turn requires reacting “said Compound 2.” In other words, the steps of the claimed methods repeatedly refer back to “said Compound” from the previous step, which in turn is used to form another compound for use in the next step or (in the case of step f)) the final product. *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1343 (Fed. Cir. 2008) (claim phrases using the term “said” refer “to the initial antecedent phrase”); *see* Ex. 10 at 1443. As a matter of logic and grammar, a skilled artisan would have understood that the recited steps in NS’s method claims must be performed in the order specified by the claims. Pentelute Decl. ¶43. Indeed, NS even gave the steps sequential lettering from a) to f), and the Compounds sequential

numbering from 1-4, reinforcing that the claims should be interpreted as requiring the recited sequence of steps. Pentelute Decl. ¶44.

Sarepta’s construction of step e) incorporates this order of steps mandated by the claim’s plain language. Pentelute Decl. ¶45. Specifically, step e) recites “reacting *said* Compound 3 with a deprotecting agent to *form* Compound 4.” By the claim’s plain language, it is logical that step d) must be carried out before step e) to obtain “*said* Compound 3.” Likewise, the reaction of step e) must “*form* Compound 4” so that step f), which uses “*said* Compound 4,” can be performed. Consistent with this, Sarepta’s construction specifies that Compound 3 used in step e) is “of step d)” and the reaction in step e) “results in Compound 4.”

Sarepta’s proposed construction is consistent with numerous cases holding that claims must be construed to require a specified sequence when recited steps refer back to prior steps. In *Kaneka Corp. v. Xiamen Kingdomway Group Co.*, for example, the Federal Circuit construed method claims for oxidizing coenzyme Q<sub>10</sub> as requiring a particular order because the oxidation step in the claims referred to “the product of the previous step.” 790 F.3d 1298, 1306-07 (Fed. Cir. 2015). Similarly, in *E-Pass Technologies, Inc. v. 3Com Corp.*, the Federal Circuit held that a claim required performing the recited steps in order because most of those steps referred back to the results of the prior step using the term “*said*.” 473 F.3d 1213, 1222 (Fed. Cir. 2007); *see also Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc.*, 152 F.3d 1368, 1375-76 (Fed. Cir. 1998) (“the sequential nature of the claim steps is apparent from the plain meaning of the claim language” reciting “*said*” element introduced in each prior step); *Bio-Rad Lab’ys, Inc. v. 10X Genomics, Inc.*, 496 F. Supp. 3d 563, 572-75 (D. Mass. 2020) (construing method claims as requiring a particular order because each of the four claimed steps referred to “*the*” product of the previous step). Like the method claims in these cases, the steps in NS’s claims also refer to the results of a prior step,

and thus the Court should construe those steps to require the specified order. *E-Pass*, 473 F.3d at 1222.

The specification supports requiring the steps to be performed in the order written. Pentelute Decl. ¶¶46-51. The *sole* synthesis scheme described in the specification follows the precise order of steps recited in the claims, listing steps a) through f) sequentially with no inserted or modified steps. *Compare* Ex. 2 at 14:1-23:56, with *id.* at claims 1 and 6; Pentelute Decl. ¶¶46-49. For instance, as Dr. Pentelute explains, Example 1, the sole example illustrating the synthesis steps used to make the PMOs, uses the identical order of steps recited in the claims. Ex. 2 at 31:32-32:67; Pentelute Decl. ¶¶46, 50. Indeed, NS appears to recognize that “the *only* embodiments in the specification of the ’322 Patent describe the method steps in the specific order as recited in the claims, with no additional steps.” *See* Br. at 32.<sup>5</sup> Nothing in the specification suggests that the claims should be construed to encompass anything other than the precise order of steps set forth in the claims. In fact, the specification expressly instructs a skilled artisan: (1) to react Compound 3 “*produced in*” step d) (corresponding to the repetition of “Step A” and “Step B” in the specification) when carrying out step e) (corresponding to “Step C” in the specification) and (2) to react Compound 4 “*produced in*” step e) “with an acid” to form a PMO when carrying out step f) (corresponding to “Step D” in the specification). Ex. 2 at 22:7-46, 23:1-39; Pentelute Decl. ¶¶49, 71; *see also Amgen Inc. v. Sandoz, Inc.*, C.A. No. 14-cv-04741-RS, 2016 WL 4137563, at \*17-18 (N.D. Cal. Aug. 4, 2016) (construing method claims as specifying that one step “occurs after”

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<sup>5</sup> Contrary to NS’s arguments, Sarepta is not importing this embodiment into the claims. *See* Br. at 32. The specification’s sole embodiment supports how a skilled artisan would have read the claims, i.e., that the claimed methods must be performed in the order as written. *Phillips*, 415 F.3d at 1313 (a skilled artisan “is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification”).

another step based on “a natural, logical order of steps” disclosed in the specification), *aff’d*, 923 F.3d 1023 (Fed. Cir. 2019).

NS asserts that Sarepta’s construction improperly imports a step order into the claims contrary to the open transitional phrase “comprising.” Br. at 29-30. Sarepta’s construction does no such thing. As discussed above, Sarepta’s construction incorporates the specific order of steps that the claim language itself mandates “as a matter of logic and grammar.” *See Mformation*, 764 F.3d at 1398. Indeed, *Kaneka*, *E-Pass*, *Mantech*, *Bio-Rad*, and *Amgen* similarly involved “comprising” claims but were held to require an order of steps because each step referred back to the product of an earlier step.

Moreover, contrary to NS’s argument, Sarepta’s construction allows additional steps to be performed before step a) (e.g., forming Compound 1 used in step a)) and/or after step f) (e.g., purifying the PMO resulting from step f)). *See Invitrogen*, 327 F.3d at 1367-70 (construing claims to a cell culturing method “comprising” steps (a) through (c) as allowing “preparatory steps in advance of step (a)’’); Pentelute Decl. ¶¶52-58. Sarepta’s construction also allows washing steps or other intermediate steps that do not chemically transform the recited compounds to different chemical compounds. Pentelute Decl. ¶¶54-57. This is also consistent with Example 1 in the specification, which employs non-transformative steps in addition to coupling each PMO monomer to the growing chain. *See, e.g.*, Ex. 2 at 31:33-32:36 (washing the chain of PMO monomers without altering the chemical structure of the chain); Pentelute Decl. ¶54.

NS cites no case holding that “comprising” overrides the order of steps mandated by the claim language and other intrinsic evidence. *See* Br. at 30-31. The case that NS relies on construed claims to methods for determining an account value comprising, *inter alia*, “determining an initial benefit payment,” “determining a subsequent periodic payment,” and “periodically determining

the account value.” *Lincoln Nat'l Life Ins. Co. v. Transamerica Fin. Life Ins. Co.*, No. 1:04-CV-396 TS, 2007 WL 710119, at \*12-13 (N.D. Ind. Mar. 6, 2007). Unlike the steps in NS’s claims, these steps lacked express language linking them in a particular order, and as such, “[t]he logic of the steps [did] not mandate the order” in which the payments were determined. *Id.* NS’s other cases do not address the impact of “comprising” on interpreting the order of steps. *See, e.g., Medichem*, 353 F.3d at 930, 933-34 (construing a process claim “comprising” a single step); *Invitrogen*, 327 F.3d at 1369-70 (allowing additional steps to be performed before steps (a) through (c) while still requiring steps (a) through (c) to be performed in order).

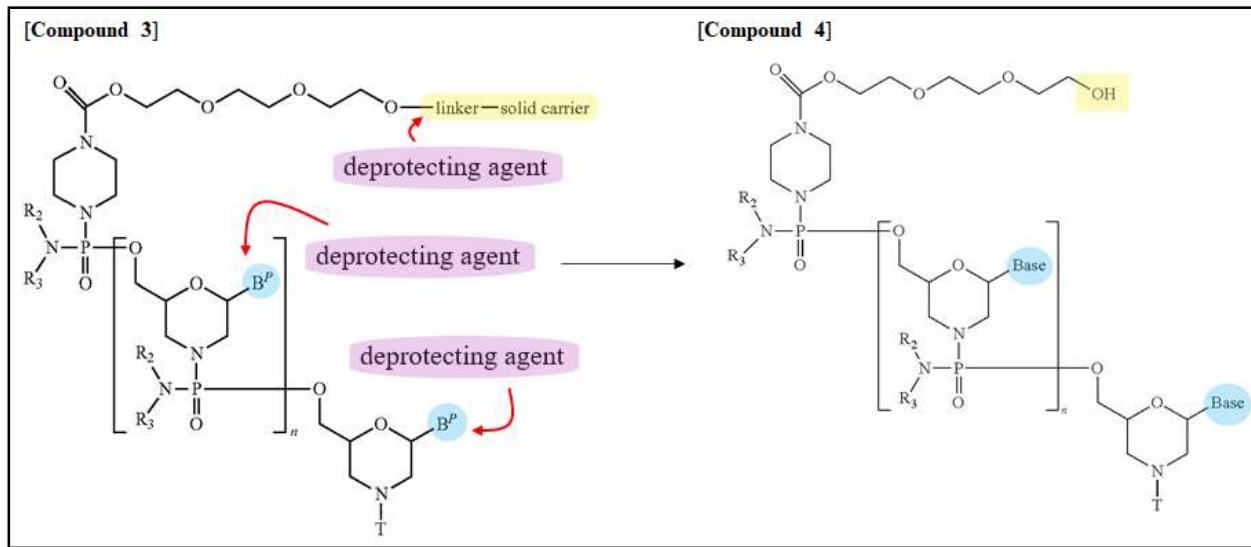
As a last resort, NS presents a hypothetical scenario that allegedly shows “why Sarepta’s proposed construction must be rejected.” Br. at 31-32. But NS’s hypothetical is not informative of a proper claim construction. Pentelute Decl. ¶59. Unlike NS’s actual claims, NS’s hypothetical claims omit the claim term “said Compound” from multiple steps. *See id.* Without this claim language linking one step to the next, NS’s hypothetical fails to track the disputed claim language and is irrelevant. *See Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (“[W]e construe the claim as written, not as the patentees wish they had written it.”).

**b. A Skilled Artisan Would Have Understood that the Claimed Deprotecting Agent Reacts Directly with Compound 3**

Step e) requires “reacting said Compound 3 with a deprotecting agent to form Compound 4.” Sarepta’s construction clarifies that Compound 3 reacts “directly” with a deprotecting agent to form Compound 4, i.e., the two compounds (Compound 3 and the deprotecting agent) chemically react to form the recited product (Compound 4). As discussed below, this is consistent with the nature of the reaction, as understood by a skilled artisan.

As illustrated below, the chemical reaction of step e) occurs because the deprotecting agent reacts *directly* with Compound 3, at each protected base (B<sup>P</sup>) and with the linker. A skilled artisan

familiar with this chemical reaction would have understood the same, i.e., that the deprotecting agent reacts directly with Compound 3, as opposed to reacting with unrecited chemical compounds in an indirect manner. Pentelute Decl. ¶¶60-64.



**Figure 2.** Schematic Representation of Step e)  
(Pentelute Decl. ¶63)

NS argues that a “direct” reaction is inconsistent with the “comprising” transitional phrase used in the claims, alleging that “a person of ordinary skill in the art would understand [directly] to mean without any other reagents or ingredients used as part of the reaction.” Br. at 28-30. But NS offers only attorney argument with no cited evidence to support the understanding of a skilled artisan. *See id.* This is insufficient. *Va. Innovation*, 614 F. App’x at 511 (“attorney arguments are not relevant intrinsic or extrinsic evidence” for claim construction).

Further, as Dr. Pentelute explains, this is *not* how a skilled artisan would understand “directly.” Pentelute Decl. ¶64; *see* Ex. 13 at 274-75. In a chemical reaction, some chemical compounds are directly involved in the reaction (e.g., Compound 3 and the deprotecting agent recited in step e)), whereas others may not chemically react but are added to facilitate the reaction (e.g., a solvent for diluting the deprotecting agent). Thus, contrary to NS’s argument, “directly”

does not exclude other reagents or ingredients used to facilitate the reaction between the recited compounds, and therefore is consistent with the claimed methods “comprising” step e).

**c. NS’s Proposed Construction is Improper**

NS proposes construing step e) as “chemically reacting Compound 3 with a deprotecting agent, in order to form Compound 4.” This construction is unsupported for several reasons.

*First*, unlike Sarepta’s construction, NS’s construction does not specify that Compound 3 in step e) was produced in step d). Pentelute Decl. ¶¶65-66. This omission is contrary to the plain language of step e), which requires reacting “*said* Compound 3” from step d), as opposed to Compound 3 from any source. *See supra* § V.B.2.a. By omitting the source of Compound 3, NS decouples step d) from step e), improperly expanding the claim to permit unrecited, transformative chemical reactions. Nothing in the claims or the specification supports that expansive scope. Ex. 2 at 22:7-67 (instructing a skilled artisan to use Compound 3 “produced in” step d)); *see* Br. at 32 (NS acknowledging that the “only embodiments in the specification” track the claimed methods); *ERBE Elektromedizin GmbH v. Int’l Trade Comm’n*, 566 F.3d 1028, 1033-34 (Fed. Cir. 2009) (rejecting a construction that was “overly broad” in light of the limited disclosures in the specification).

*Second*, NS’s construction characterizes Compound 4 as simply a goal of step e) (“in order to form Compound 4”), rather than a result that must be achieved as in Sarepta’s construction (“which results in Compound 4”). Pentelute Decl. ¶67. NS’s construction is contrary to the plain language of step e), which requires reacting Compound 3 with a deprotecting agent “*to form* Compound 4.” NS’s construction is also illogical because Compound 4 must result from step e); otherwise, step f) that follows step e) and uses “*said* Compound 4” cannot be performed. *See supra* § V.B.2.a. NS’s construction, if adopted, would allow additional, unrecited transformative chemical reactions between step e) and step f) to obtain Compound 4, which again is improper in

light of the plain language of the claims and the limited disclosure in the specification. *See, e.g.*, Ex. 2 at claims 1 and 6, 14:1-23:56, 31:32-32:67.

*Third*, NS's construction does not require Compound 3 to react directly with the recited deprotecting agent. By not specifying the nature of this chemical reaction, NS's construction sweeps in chemical reactions in which Compound 3 and the deprotecting agent “indirectly” react. Pentelute Decl. ¶68. For example, under NS's construction, step e) would arguably encompass a reaction in which Compound 3 reacts with an unrecited compound X, resulting in another unrecited compound Y, which then reacts with a deprotecting agent. This is contrary to a skilled artisan's understanding of step e) (*see supra* § V.B.2.b), and moreover, extends well beyond what is disclosed in the specification, as NS admits. *See* Br. at 30 (NS acknowledging that “the *only* embodiment in the '322 Patent” reacts “the deprotecting agent directly with Compound 3”).

In sum, NS's overly expansive construction, which is unsupported by the intrinsic and extrinsic evidence and applicable law, should be rejected. *See Phillips*, 415 F.3d at 1312-19.

### 3. NS's Reply Position

#### a. Term 2 Does Not Require an Order to the Claimed Steps

It is a general canon of claim construction that “[a]bsent affirmative indication to the contrary, method steps need not be performed in the order in which they are recited.” *Cybersettle*, 243 Fed. Appx. at 603. Sarepta argues that here the language and structure of the claims requires the steps to be performed in the order written. Br. at 33-38. Sarepta's argument relies primarily on (i) the fact that certain steps in the claim use proper antecedent basis to refer to “said Compound[s]” listed in previous steps and (ii) various case law that dealt with unrelated disputes as to whether steps could be performed simultaneously. Importantly, Sarepta ignores the clear language of the claimed method—which uses open “comprising” language. “The transition ‘comprising’ in a **method claim** indicates that the claim is open-ended and **allows for additional**

*steps.”* *Medichem*, 353 F.3d at 933 (quoting *Invitrogen*, 327 F.3d at 1368) (emphasis added). The availability of these additional steps is dispositive in this case.

First, Sarepta misstates the meaning of the claim’s use of “said Compound.” Br. at 34-35. According to Sarepta, the use of the word “said” means that “said Compound” refers to a specific previous Compound—the exact Compound that was previously referenced:

6. A solid-phase method of making a phosphorodiamidate morpholino oligomer (PMO) . . . said method comprising:

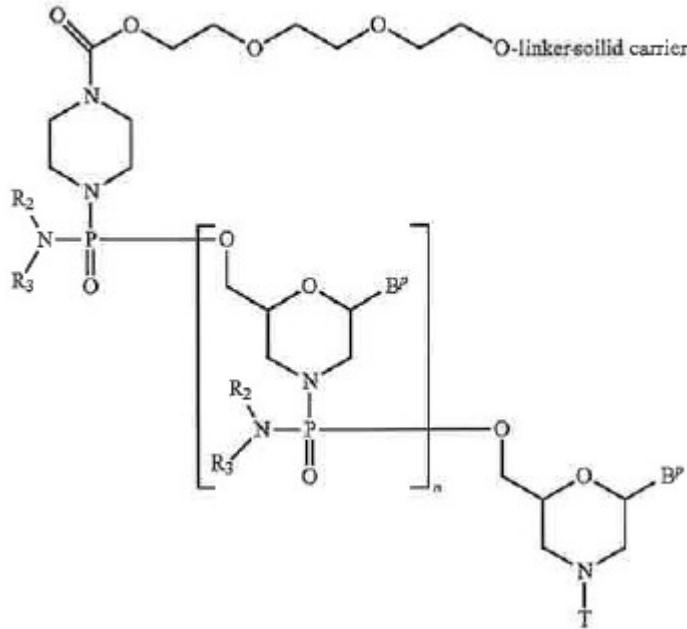
- a) providing Compound 1: . . . ;
- b) reacting said Compound 1 with an acid to form Compound 2;
- c) reacting said Compound 2 with a morpholino monomer in the presence of a base and a solvent;
- d) repeating steps b) and c) until Compound 3 is complete;
- e) reacting said Compound 3 with a deprotecting agent to form Compound 4; and
- f) reacting said Compound 4 with an acid to form said PMO: . . . .

*Id.* But, when the use of the word “said” is simply “refer[ing] back to an earlier phrase in the claim, the scope of the term will be the same as the scope of the earlier language.” *Takeda Pharm. Co. v. Sandoz, Inc.*, No. 12-00446 JCS, 2013 U.S. Dist. LEXIS 70469, at \*18 (N.D. Cal. May 16, 2013) (citing *Baldwin*, 512 F.3d at 1343). In other words, a POSA would understand that “said” is used as a shorthand so that the specific “Compound” does not have to be separately defined and identified each time the word is used—the same *definition* of the compound applies throughout the claim. Ex. 15 ¶¶28-30, 51-54.

For example, Claim 1 of the ’322 Patent provides step d), and defines “Compound 3” therein using a chemical drawing:

d) repeating steps b) and c) until Compound 3 is complete;

[Compound 3]



Ex. 2 at cl. 1. Claim 1 then describes “said Compound 3” in step e):

e) reacting said Compound 3 with a deprotecting agent to form Compound 4; and

*Id.* A POSA would have understood that reacting “said Compound 3” would not necessarily require reacting the exact compound that is formed by step d), but instead **would require reacting Compound 3 as it was previously defined**—a Compound 3 having the same chemical structure as shown in the claim. Ex. 15 ¶¶28-30, 51-54, 62. Accordingly, the claims’ use of “said Compound” does not necessitate an order to the claimed steps.

This specific method of defining the various “Compounds” of the relevant claims also demonstrates why the case law relied on by Sarepta is inapplicable to the analysis here. In each case, the products of the method steps are defined by the step used to form the product, not by their chemical structure. Br. at 35-36 (citing *Kaneka*, 790 F.3d at 1306-07; *E-Pass*, 473 F.3d at 1222, *Mantech*, 152 F.3d at 1375-76, and *Bio-Rad*, 496 F. Supp. 3d at 572-75). For example, the claims

in *Kaneka* recited “obtain[ing] reduced coenzyme Q10” and “oxidizing ***thus-obtained*** reduced coenzyme Q10.” 790 F.3d at 1301. Similarly, the claims in *E-Pass* included the steps of “[i] transferring a data set...[and ii] storing said transferred data set.” 473 F.3d at 1216. In each of these cases, it was impossible to perform the later step without first performing the earlier step because the subject of the later step was necessarily formed by the earlier step. Thus, an order to the step was required.

The claims of the '322 Patent are different. Here, the subject of each of the steps is a Compound that is ***defined by a chemical structure or diagram***—not by how that Compound is formed. Ex. 15 ¶¶28-30, 51-54. Accordingly, a POSA would have understood that each of the subject Compounds (e.g., “said Compound 3” in “step e”) could have been obtained using a variety of unrecited steps. “***Since the claim is not foreclosed to additional steps, the steps themselves are not foreclosed from being carried out in a different order than stated in the claim.***” *Lincoln Nat'l*, 2007 U.S. Dist. LEXIS 16822 at \*35.

As explained in NS's Opening Brief, Method B (shown below) includes additional steps that demonstrate that Sarepta's proposed construction cannot be adopted:

Step Number	Method A (Only Claimed Steps)	Method B (Additional Unrecited Steps)
1	Step a) – Providing Compound 1	Step a) – Providing Compound 1
2	Step b) – Forming Compound 2	Step b) – Forming Compound 2
3	Step c) – Reacting Compound 2 with a monomer	Step c) – Reacting Compound 2 with a monomer
4	Step d) – repeating steps b) and c) to form Compound 3	Step d) – repeating steps b) and c) to form Compound 3
5		Reacting Compound 3 with a reagent to form an intermediate.
6		Reacting the intermediate with a second reagent to re-form Compound 3.
7	Step e) – Reacting Compound 3 with reagent to form Compound 4	Step e) – Reacting Compound 3 with reagent to form Compound 4
8	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO

As Dr. Luedtke explains, additional steps 5 and 6 in Method B could take a variety of forms. Ex. 15 ¶¶55-62. For example, a POSA could perform a simple reaction during Step 5 (e.g., removing the trityl group of Compound 3), then reverse that reaction in Step 6 (e.g., adding the trityl group back to the same position to re-form Compound 3). *Id.* ¶¶58-59. Under Sarepta’s proposal, the inclusion of such steps would avoid infringement because step e) would not use the Compound 3 that was the result “of step d”—instead step e) would use Compound 3 of an unrecited step. *Id.* Such a result is clearly wrong. Alternatively, a POSA could use Steps 5 and 6 to change the linker and/or solid carrier of Compound 3. *Id.* ¶¶60-61. For example, the linker of Compound 3 could be modified during Steps 5 and 6. *Id.* Again, under Sarepta’s proposed construction, the inclusion of such steps would avoid infringement because step e) would not use the Compound 3 that was the result “of step d”—instead step e) would use Compound 3 of a different, unrecited step. *Id.*

Due to the plain language of the claims, and the fact that the claims define the various “Compounds” by chemical structure rather than by the method used to form the “Compound,” a POSA would understand that “*said* Compound” does not refer to a Compound formed by a specific step, but instead refers to a Compound having a specific structure. Ex. 15 ¶¶28-30, 51-62. As such, Sarepta’s construction of Term 2, which requires using “Compound 3 of step d),” must be rejected.

**b. Sarepta’s Importation of “Directly” Into the Claim is Improper**

Sarepta’s proposed construction for Term 2 also requires “that the deprotecting agent reacts directly with Compound 3.” Br. at 38-40. Sarepta confirms that, under its construction, Compound 3 and the deprotecting agent can be the only compounds involved in the reaction—other unrecited compounds can only serve to facilitate the reaction, not actually react. *Id.* at 39-40 (“some chemical compounds are directly involved in the reaction (e.g., Compound 3 and the deprotecting agent recited in step e)), whereas others may not chemically react but are added to facilitate the reaction (e.g., a solvent for diluting the deprotecting agent)”). Sarepta’s position is clearly untenable and must be rejected. First, claim construction “begins with the words of the claim.” *Wi-Lan*, 811 F.3d at 462. The claim itself uses only the word “reacting” without limiting the reagents involved. Second, the disputed claims use broad “comprising” language as the transitional phrase. *See* ’322 Patent cls. 1, 6 (using the transition “said method comprising”); Ex. 15 ¶40. The use of “‘comprising’ creates a presumption that the recited elements are only a part of the [invention], that *the claim does not exclude additional, unrecited elements.*” *Multilayer Stretch*, 831 F.3d at 1358 (quoting *Crystal Semiconductor*, 246 F.3d at 1348). This precedent demonstrates that Sarepta’s proposed construction must be rejected.

Moreover, step b) of the disputed claims contains nearly identical language as step e).

- b) reacting said Compound 1 with an acid to form Compound 2;
- e) reacting said Compound 3 with a deprotecting agent to form Compound 4; and

'322 Patent, cl. 1. If step e) requires reacting Compound 3 "directly" with a deprotecting agent (as Sarepta proposes), then step b) must also require reacting Compound 1 "directly" with an acid, which is clearly incorrect. *Cloud Farm Assocs. LP v. Volkswagen Grp. of Am., Inc.*, 674 F. App'x 1000, 1006 (Fed. Cir. 2017) ("The same term should be construed consistently throughout the same patent."). As Dr. Luedtke explains, a POSA would have understood that the examples and descriptions of step b) in the '322 Patent describe step b) as including multi-step and/or indirect reactions. Ex. 15 ¶¶41-49. Accordingly, a POSA would have understood that the plain and ordinary meaning of "reacting said Compound" in the context of both step b) and the nearly identical step e) would not require a "direct" reaction and that Sarepta's construction, when consistently applied would, in fact, exclude preferred embodiments and examples described in the '322 Patent. As such, it must be rejected. *GE Lighting*, 750 F.3d at 1311 ("[W]here claims can reasonably [be] interpreted to include a specific embodiment, it is incorrect to construe the claims to exclude that embodiment.").

**c. Sarepta's Criticisms of NS's Proposed Construction Are Baseless**

As explained in NS's Opening Brief, NS's proposal gives the disputed term its plain and ordinary meaning as required by general claim construction principles. Sarepta arguments otherwise do not pass muster.

Sarepta's first argument—that "said Compound 3" requires using Compound 3 from a specific source (e.g., step d)), is not supported. *See* Br. at 40-41. As discussed above, the

terminology “said Compound 3” simply requires that Compound 3 have the same chemical structure that was used to define the Compound—it does not refer to any source. Ex. 15 ¶¶28-30, 51-62. Similarly, Sarepta’s addition of “directly” does not match the claim language and is unfounded. *Id.* ¶¶40-49.

Sarepta’s second argument—that “NS’s construction characterizes Compound 4 as simply a goal of step e)” is also unfounded. Br. at 40-41. NS does not dispute that step e) must result in the formation of Compound 4. To the extent the Court believes that NS’s construction is unclear, NS is willing to adopt language confirming that the reaction of step e) “results in Compound 4.”

#### **4. Sarepta’s Sur-Reply Position**

##### **a. Sarepta’s Construction Conforms to the Intrinsic Evidence**

NS argues that absent affirmative indication to the contrary, method steps need not be performed in order. Br. at 41 (citing *Cybersettle*, 243 F. App’x at 609). The intrinsic evidence here, however, includes numerous affirmative indications that the claims require the specified order of steps. Br. at 33-37; Pentelute Rep. Decl. ¶¶8-22. Step a) *provides* “Compound 1” and each subsequent step uses “*said Compound*” provided in the prior step to form another compound used in the next step (or the final product). These steps are alphabetically labeled from “a)” to “f),” and the compounds formed in each step are sequentially numbered from “Compound 1” to “Compound 4.” The specification’s sole synthesis scheme follows the order of steps listed in the claims and requires reacting each compound “produced in” the previous step. Consistent with this intrinsic evidence, Sarepta’s construction of step e) specifies using Compound 3 from the prior step, which results in Compound 4 used in the final step f). Even NS’s expert acknowledges that “steps a) through d) must be performed in the listed order.” Luedtke Decl. ¶33.

NS argues that the open transitional phrase “comprising” allows additional steps. Br. at 41-42. But *Kaneka*, *E-Pass*, *Mantech*, *Bio-Rad*, and *Amgen* all involved “comprising” claims

construed to *require* the listed order of steps because of similar affirmative indicia. Br. at 37-38. Moreover, Sarepta’s construction gives effect to the term “comprising,” as it allows additional steps to be performed that do not chemically transform the recited compounds. *Id.*; Pentelute Decl. ¶¶52-58.

NS also argues that “*said* Compound” refers to any compound having the recited chemical structure regardless of how it was made. Br. at 42-43. For example, NS contends that step e) does not require Compound 3 from step d), but instead encompasses use of “*a* Compound 3” from any source. *Id.* But this interpretation is contrary to the claim language, which refers to “*said* Compound 3” made in the prior step. Had the applicant intended to refer only to the previously defined structure, reciting “Compound 3” would have been more appropriate. By conflating “*a*” and “*said*,” NS renders the claim term “*said*” meaningless. *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006). NS’s interpretation is also contrary to the specification, which identifies step d) as the *sole* source for Compound 3. Pentelute Decl. ¶¶47-50; Pentelute Rep. Decl. ¶25.

*Eastman Chemical Co. v. BASF Aktiengesellschaft* is instructive. 47 F. App’x 566 (Fed. Cir. 2002). Like NS’s claims, the claims in *Eastman* recited a stepwise method “comprising” a series of listed steps. Step (a) involved producing a “salt” of Formula (III) (a compound defined by its chemical structure), and step (c) involved reacting “the salt” with an acid. *Id.* at 567-68. The Federal Circuit held that “the salt” in step (c) referred to the salt . . . *produced in step (a)*” because the plain language showed that “the term refers to the salt earlier described.” *Id.* at 573-74. The specification lacked any indication of “salts formed in a manner not taught in step (a).” *Id.* While the patentee, like NS, advocated that “the salt” could refer to salts formed by another method, the court rejected that position as rendering “the” meaningless. *Id.* A similar analysis should apply here.

NS argues that, unlike prior cases, each of the “Compounds” here is defined by a chemical structure, “not by how that Compound is formed.” Br. at 44. NS’s claims, however, define the “Compounds” both by structure and how they are made. Pentelute Rep. Decl. ¶¶10-16. Further, in *Eastman*, “the salt” in step (c) was construed as the salt *produced in step (a)*, even though step (a) included a chemical structure (formula III). *Eastman*, 47 F. App’x at 573-74. Similarly, in *Bio-Rad*, the court construed each step to refer to “the” product of the previous step even though the products were not defined by how they were made. 496 F. Supp. 3d. at 572-74; *see also Mantech*, 152 F.3d at 1370 ((a) providing “wells” and (b) generating a test flow “from one of *said wells*”); *Amgen*, 2016 WL 4137563, at \*17-18 (“(c) washing the separation matrix” and “(d) eluting the protein from *the separation matrix*”). Thus, the meaning of “*said Compound*” should not change irrespective of whether the compound is defined by structure, how it is made, or both—the plain language of step e) expressly refers to Compound 3 of step d). Pentelute Rep. Decl. ¶¶23-26.

NS’s hypothetical scenario (Br. at 44-45) remains irrelevant because it omits the term “*said*” and therefore does not correspond to the claim language. Br. at 38. The hypothetical is also inconsistent with the specification, which identifies step d) as the *sole* source for obtaining Compound 3. Pentelute Decl. ¶¶47-50; Pentelute Rep. Decl. ¶¶27-31.

**b. Sarepta’s Construction Reflects the Nature of the Reaction**

Sarepta’s construction clarifies that Compound 3 reacts “directly” with a deprotecting agent in step e). This is consistent with plain language of step e), which states “reacting *said Compound 3 with a deprotecting agent*,” i.e., directly—no other intermediate, indirect reactions are recited. Pentelute Rep. Decl. ¶¶32-33. The specification likewise exclusively depicts a *direct* reaction between Compound 3 and a deprotecting agent. *Id.*; Ex. 2 at 22:7-67.

NS argues that a different step (step b)) can encompass “multi-step and/or indirect reactions.” Br. at 47. NS is wrong about both steps b) and e). Pentelute Rep. Decl. ¶¶34-44. The “multi-step and/or indirect reactions” discussed by NS for step b) each involve the *direct* reaction between Compound 1 and an acid. *Id.* Similarly, for step e)—even if some “multi-step and/or indirect reactions” are theoretically possible (NS and Dr. Luedtke identified none (Br. at 46-47; Luedtke Decl. ¶¶37-49)), Compound 3 and the deprotecting agent would still react *directly*. Sarepta’s construction permits additional non-transformative reagents/reactions (such as those identified by NS (Br. at 46)), rendering NS’s criticism irrelevant. Pentelute Decl. ¶¶52-58, 64.

**c. NS’s Construction Is Impermissibly Broad**

Step e) recites “reacting *said* Compound 3 *with* a deprotecting agent.” NS’s construction impermissibly broadens the claims. First, it allows use of *a* Compound 3 from *any* source, instead of Compound 3 as synthesized in step d). Second, it encompasses *indirect* chemical reactions (i.e., reacting Compound 3 with something else to form a new compound, which in turn is reacted with a deprotecting agent). Third, NS’s construction allows step e) to be performed out of sequence. Pentelute Rep. Decl. ¶¶45-48.

NS’s attempt to expand the claims beyond what logic, their plain language, and the specification discloses is improper. *See Howmedica Osteonics Corp. v. Zimmer, Inc.*, 822 F.3d 1312, 1320-22 (Fed. Cir. 2016) (adopting narrow construction because “every description and every figure in the patent” discussed claim term narrowly); *Regeneron Pharm., Inc. v. Merus B.V.*, No. 14 Civ. 1650 (KBF), 2014 WL 6611510, at \*15 (S.D.N.Y. Nov. 21, 2014) (holding that claim construction principles precluded reading a term as having a broader meaning than implicitly or explicitly disclosed in the patent).

**C. Term 3: “f) reacting [said] Compound 4 with an acid to form said oligomer [or PMO]”**

<b>Term</b>	<b>NS’s Position</b>	<b>Sarepta’s Position</b>
<p><b>“f) reacting Compound 4 with an acid to form said oligomer”</b>            (’322 Patent Claim 1)</p> <p>or <b>“f) reacting said Compound 4 with an acid to form said PMO”</b>            (’322 Patent Claim 6)</p>	Plain and ordinary meaning – i.e., chemically reacting Compound 4 with an acid, in order to form the oligomer [or the PMO]	Plain and ordinary meaning, i.e., chemically reacting an acid directly with Compound 4 of step e), which results in the oligomer or the PMO. Step f) must occur after step e).

**1. NS’s Opening Position**

The analysis for Term 3 is nearly identical to the analysis with respect to Term 2. Once again, NS’s proposal gives the disputed term its plain and ordinary meaning as required by general claim construction principles. *Home Diagnostics*, 381 F.3d at 1355, 1357; *Phillips*, 415 F.3d at 1312–13; *Voda*, 536 F.3d at 1319. As agreed by both parties, the plain and ordinary meaning of the term “f) reacting Compound 4 with an acid to form said oligomer [or PMO]” requires “chemically reacting” at least two ingredients—Compound 4 and an acid—in order to form a specific result—the oligomer or PMO. Like with Term 2, NS’s proposed construction is constrained to the plain and ordinary meaning and should be adopted, but Sarepta’s proposed construction includes additional limitations that are not found in the plain and ordinary meaning of the disputed term.

Again, Sarepta includes a requirement that the two ingredients be reacted “directly” together—i.e., without any other reagents or ingredients used as part of the reaction. Moreover, Sarepta once again attempts to import step order into the claim by (i) requiring that one of the ingredients—Compound 4—be the result of another step of the method claim (step e), and (ii)

requiring that “Step f) must occur after step e).” Since none of Sarepta’s proposed additions are supported by the relevant case law or the intrinsic record, Sarepta’s proposed construction should be rejected.

Like with Term 2, Sarepta’s additional limitations must be rejected because the relevant claims use the broad language “comprising” as their transitional phrase. *See* Ex. 2 at claims 1 and 6 (using the transition “said method comprising”). As before, the use of “‘comprising’ creates a presumption that the recited elements are only a part of the device, that ***the claim does not exclude additional, unrecited elements.***” *Multilayer Stretch*, 831 F.3d at 1358 (quoting *Crystal Semiconductor*, 246 F.3d at 1348). As explained above, by requiring that the disputed term includes “chemically reacting an acid ***directly*** with Compound 4,” Sarepta improperly excludes “additional, unrecited” reagents or ingredients from the step. Here, the use of “comprising” as the transitional phrase specifically permits such “indirect” reactions. Even if Sarepta argues that the only embodiment in the ’322 Patent includes reacting the acid directly with Compound 4, its argument would be unsuccessful. *GE Lighting*, 750 F.3d at 1308-10 (Fed. Cir. 2014) (“[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment . . .”); *Fiber Optic*, 172 F. App’x at 997 (“[T]he standard rule [is] that a claim construction should decline to incorporate additional limitations from the specification.”). Since the plain and ordinary meaning of the disputed term does not require Compound 4 to be reacted “directly” with an acid, Sarepta’s proposed construction must be rejected.

Similarly to Term 2, the claims’ use of “comprising” is also fatal to Sarepta’s improper importation of a step order into the claims. With respect to Term 3, Sarepta attempts to import claim order into the claims in two ways—by requiring Compound 4 to be “of step e)” and by expressly requiring that “step f) must occur after step e).” However, “[a]bsent affirmative

indication to the contrary, method steps need not be performed in the order in which they are recited.” *Cybersettle*, 243 Fed. Appx. at 603. Again, Sarepta will likely argue that the claim language of the methods steps themselves implicitly require that they be practiced in a specific order. *See* Ex. 2 at claims 1 and 6 (step a) starting with Compound 1; step b) reacting Compound 1 as an ingredient to form Compound 2; etc.). Sarepta’s argument again fails because, here, the claims use “comprising,” and “[t]he transition ‘comprising’ in a **method claim** indicates that the claim is open-ended and **allows for additional steps.**” *Medichem*, 353 F.3d at 933 (quoting *Invitrogen*, 327 F.3d at 1368. Like with Term 2, “*[s]ince the claim is not foreclosed to additional steps, the steps themselves are not foreclosed from being carried out in a different order than stated in the claim.*” *Lincoln Nat'l*, 2007 U.S. Dist. LEXIS 16822 at \*35.

Once again, a comparison of two methods—one using only the steps set forth in claims 1 and 6 of the ’322 Patent, and one including additional steps—is helpful:

Step Number	Method A (Only Claimed Steps)	Method B (Additional Unrecited Steps)
1	Step a) – Providing Compound 1	Step a) – Providing Compound 1
2	Step b) – Forming Compound 2	Step b) – Forming Compound 2
3	Step c) – Reacting Compound 2 with a monomer	Step c) – Reacting Compound 2 with a monomer
4	Step d) – repeating steps b) and c) to form Compound 3	Step d) – repeating steps b) and c) to form Compound 3
5	Step e) – Reacting Compound 3 with reagent to form Compound 4	Conducting a series of reactions (not a single reaction using a deprotecting agent) to form Compound 4.
6	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO
7		Conducting a series of reactions to reform Compound 3

8		Step e) – Reacting Compound 3 with reagent to form Compound 4
9		Conducting a series of reactions (not a single reaction using an acid) to form the Oligomer or PMO.

Again, each of these methods practice all of the steps of claims 1 and 6. Indeed, Method B practices each of the steps even though step f) occurs before step e) and uses Compound 4 from a different step. Thus, adding Sarepta’s proposed limitations, that step f) requires using Compound 4 “of step e)” and that “step f) must occur after step e)” would improperly result in Method B no longer practicing all of the steps. Again, this clearly erroneous result shows why Sarepta’s proposed construction must be rejected.

Even if Sarepta again argues that the only embodiments in the specification of the ’322 Patent describe the method steps in the specific order as recited in the claims, with no additional steps, its argument must be similarly rejected. *GE Lighting*, 750 F.3d at 1308-10 (“[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment . . .”); *Fiber Optic*, 172 F. App’x at 997 (“[T]he standard rule [is] that a claim construction should decline to incorporate additional limitations from the specification.”).

Since NS’s proposed construction gives the disputed phrase its plain and ordinary meaning and Sarepta’s proposed construction imports additional limitations contrary to claim construction principles, NS’s proposed construction should be adopted and Sarepta’s proposed construction should be rejected.

## **2. Sarepta’s Answering Position**

The issues for step f) are similar to those for step e) addressed above. As with step e), Sarepta’s construction of step f) requires the steps to be performed in the order written. Pentelute

Decl. ¶¶69-70. Sarepta’s construction also reflects the nature of this reaction, i.e., Compound 4 must react directly with an acid resulting in the formation of the PMO. *Id.*

**a. The Recited Steps Must Be Performed in the Order Written**

The claim language and structure of the claims make it clear that the recited steps must be performed in the order written. *See supra* § V.B.2.a; Pentelute Decl. ¶¶71, 42-44. The recited steps are linked to one another, repeatedly referring back to “said Compound” from the previous step, which in turn is used to form another compound for use in the next step or (in the case of step f) the final product. *See supra* § V.B.2.a. The sole synthesis scheme reported and exemplified in the specification also follows the precise order of steps recited in the claims, listing steps a) through f) with no inserted or modified transformative chemical reactions. *Compare* Ex. 2 at 14:1-23:56, 31:32-32:67, *with id.* at claims 1 and 6; Pentelute Decl. ¶¶71, 46-51. Construing method claims like NS’s, courts have consistently required an ordering of steps where the claim language required a particular order of steps as a matter of logic and grammar. *See, e.g., Kaneka*, 790 F.3d at 1306-07; *Mformation*, 764 F.3d at 1398-400; *E-Pass*, 473 F.3d at 1221-22; *Mantech*, 152 F.3d at 1375-76; *Bio-Rad*, 496 F. Supp. 3d at 572-75; *Amgen*, 2016 WL 4137563, at \*17-18.

Sarepta’s construction of step f) therefore incorporates the order of steps mandated by the claim’s plain language and the specification. Pentelute Decl. ¶71. For example, step f) of claim 6 recites “reacting *said* Compound 4 with an acid to form *said* PMO.” Ex. 2 at claim 6. By the plain language, it is logical that step e) must be carried out before step f) to obtain “*said* Compound 4.” Pentelute Decl. ¶71. Likewise, the reaction of step f) must “*form said* oligomer [or PMO]” to complete the claimed PMO. Ex. 2 at claims 1 and 6 (reciting a “solid-phase method of making an oligomer [or a PMO]”). This requisite order of steps is also clear from the specification, which (1) instructs a skilled artisan to react Compound 4 “*produced in*” step e) (corresponding to “Step C” in the specification) when carrying out step f) (corresponding to “Step D” in the specification)

and (2) states that a PMO is “produced by” the reaction. Ex. 2 at 23:1-39. Consistent with the intrinsic evidence, Sarepta’s construction specifies that Compound 4 used in step f) is “of step e)” and the reaction in step f) “results in the oligomer or the PMO.” *See Amgen*, 2016 WL 4137563, at \*17-18.

It is immaterial that step f) in claim 1 does not expressly refer to “said” Compound 4. Pentelute Decl. ¶72. Sarepta’s construction specifying that “step f) must occur after step e)” conforms to the specification’s express teaching that Compound 4 “produced in” step e) must be used in the reaction in step f). Ex. 2 at 23:1-39. As a matter of logic, it also makes sense to construe step f) as the final step of the claimed method because the step leads to the formation of the claimed “PMO” or “oligomer.” Courts in analogous situations have required claims to be performed in the order written. *See Amgen*, 923 F.3d at 1028 (affirming a district court’s construction specifying that one step “must occur after” another step when the claim’s plain language logically required a sequence of process steps and the specification consistently described the process as a sequence of steps); *E-Pass*, 473 F.3d at 1221-22 (construing a method claim to require an order of steps where most of the steps referred to the completed results of a prior step).

NS again asserts that Sarepta’s construction improperly imports a step order into the claims in conflict with the open transitional phrase “comprising.” Br. at 53-54. But Sarepta’s construction does not import any limitation into the claims; it incorporates the order of steps mandated by the claim language “as a matter of logic and grammar.” *See Mformation*, 764 F.3d at 1398-400. Nor does Sarepta’s construction exclude any additional step that could be performed before step a) or after step f) or any intermediate steps (such as washing steps) that do not transform the recited

compounds to different chemical compounds. *See Invitrogen*, 327 F.3d at 1367-70; Pentelute Decl. ¶¶73-75.

Unlike the '322 patent claims, the "comprising" claims in NS's cited cases lacked express language linking the steps in a particular order. *See Br. at 53-54; Lincoln Nat'l*, 2007 WL 710119, at \*12-13 ("The logic of the steps does not mandate the order."). Other cases relied on by NS did not address the impact of "comprising" on interpreting the order of steps or involved only a single step. *See, e.g., Medicchem*, 353 F.3d at 929, 933-34 (construing a process claim "comprising" a single step); *Invitrogen*, 327 F.3d at 1369-70 (allowing additional steps to be performed before steps (a) through (c) while still requiring steps (a) through (c) to be performed in order).

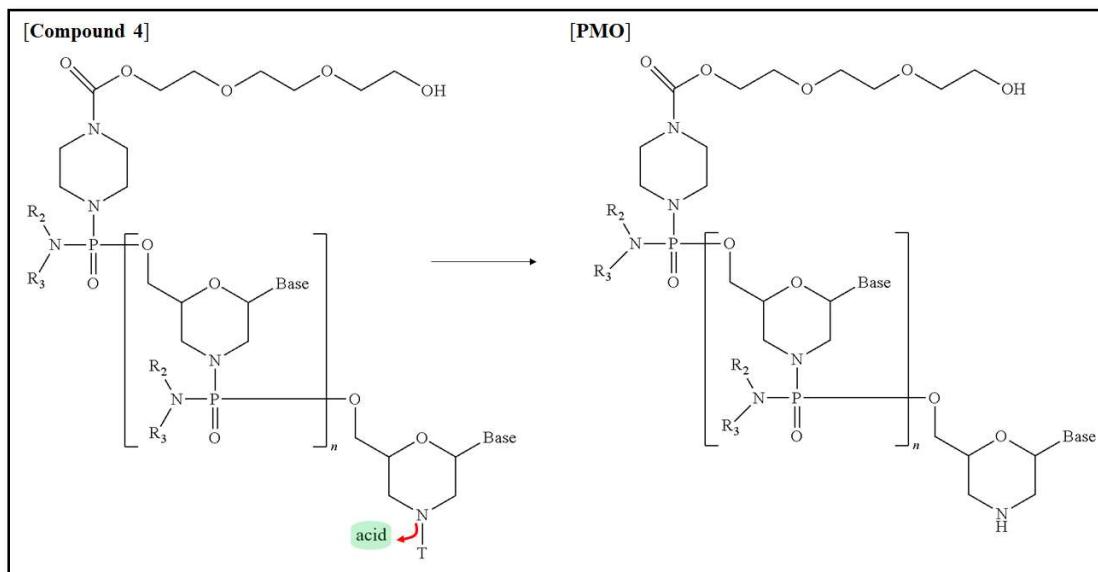
As with step e), NS raises an inapposite hypothetical scenario. *See Br. at 54-55*. Like the hypothetical that NS presented for step e), NS's hypothetical here omits the '322 patent's repeated references to "said Compound" from a preceding step, making it irrelevant to the issues in this case. *See Chef Am.*, 358 F.3d at 1374 (a claim must be construed "as written," not as the patent owner wishes it had been written); Pentelute Decl. ¶76.

**b. A Skilled Artisan Would Have Understood that Acid Reacts Directly with Compound 4**

Step f), the final step of the claimed method, requires "reacting said Compound 4 with an acid to form said PMO." Sarepta's construction clarifies that Compound 4 reacts "directly" with an acid to form the PMO. As discussed below, this is consistent with the nature of the reaction, as understood by a skilled artisan.

As illustrated below, Compound 4 is protected at its 3'-nitrogen (N) with a chemical group known as a trityl group (T). The chemical reaction in step f) occurs because the acid reacts directly with Compound 4, at the protected 3'-nitrogen. A skilled artisan familiar with this chemical reaction would have understood the same, i.e., that the acid reacts directly with Compound 4, as

opposed to reacting with unrecited chemical compounds that then interact with Compound 4. Pentelute Decl. ¶¶77-81.



**Figure 3.** Schematic Representation of Step f)  
(Pentelute Decl. ¶80)

As with step e), NS argues that a “direct” reaction is inconsistent with the “comprising” transitional phrase used in the claims because “directly” means “without any other reagents or ingredients used as part of the reaction.” *See supra* § V.B.2.b; Br. at 52-53. But NS offers nothing but attorney argument to support a skilled artisan’s understanding, which is insufficient. *See* Br. at 52-53; *Va. Innovation*, 614 F. App’x at 511 (“attorney arguments are not relevant intrinsic or extrinsic evidence” for claim construction). Further, as Dr. Pentelute explains, this is *not* how a skilled artisan would understand “directly.” Pentelute Decl. ¶81; *see* Ex. 13 at 274-75. Contrary to NS’s position, “directly” does not exclude other reagents or ingredients used to facilitate the reaction, and therefore is consistent with the claimed method “comprising” step f).

**c. NS's Proposed Construction Is Improper**

NS proposes construing step f) as “chemically reacting Compound 4 with an acid, in order to form the oligomer [or the PMO].” As with its construction of step e), NS’s construction of step f) would improperly expand the scope of the claims beyond their plain and ordinary meaning.

*First*, unlike Sarepta’s construction, NS’s construction does not specify that Compound 4 used in step f) was produced in step e). Pentelute Decl. ¶¶82-84. This omission is contrary to the intrinsic evidence and the explicit claim language that mandates the order of steps, i.e., reacting “said” Compound 4 “produced in” step e), as opposed to Compound 4 from any source. *See supra* § V.C.2.a. By omitting the source of Compound 4, NS decouples step e) from step f), improperly permitting unrecited transformative chemical reactions. Nothing in the claim language or the specification’s limited disclosure supports that expansive claim scope. Ex. 2 at 23:1-56 (instructing a skilled artisan to use Compound 4 “produced in” step e)); *ERBE Elektromedizin*, 566 F.3d at 1033-34 (rejecting a construction that is “overly broad” in light of the limited disclosures in the specification).

*Second*, NS’s construction characterizes the PMO or oligomer as simply a goal of step f) (“in order to form the oligomer or the PMO”), rather than as a result that must be achieved as in Sarepta’s construction (“which results in the oligomer or the PMO”). Pentelute Decl. ¶85. NS’s construction is contrary to the plain language of step f), which requires reacting Compound 4 with an acid “*to form said oligomer [or PMO]*.” It is also inconsistent with the specification’s express statement that “PMO (I) is produced by reacting Compound [4] . . . with an acid.” Ex. 2 at 23:1-56.

*Third*, NS’s construction does not require Compound 4 to react directly with the recited acid. Pentelute Decl. ¶86. By omitting the nature of this chemical reaction, NS’s construction sweeps in chemical reactions in which Compound 4 and the acid “indirectly” react. For example,

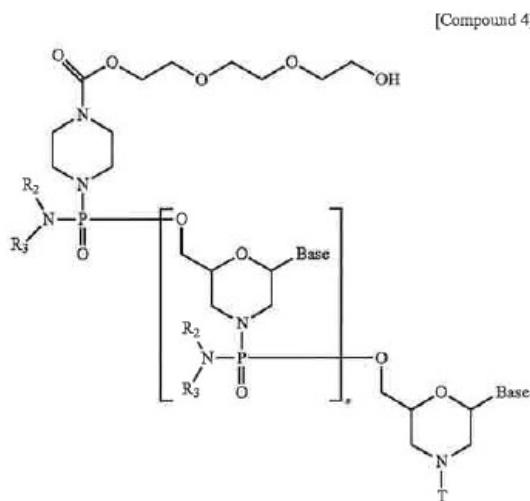
under NS's construction, step f) would arguably encompass a reaction in which Compound 4 reacts with an unrecited compound X, resulting in another unrecited compound Y, which then reacts with an acid to form the PMO. This is contrary to a skilled artisan's understanding of step f) (*see supra* § V.C.2.b), and moreover, extends well beyond the specification's limited disclosure.

In sum, the Court should reject NS's overly expansive construction, which is unsupported by the intrinsic and extrinsic evidence and applicable law. *See Phillips*, 415 F.3d at 1312-19.

### 3. NS's Reply Position

Sarepta's arguments for Term 3 are nearly identical to those for Term 2 and must be rejected for the same reasons. Once again, NS's proposal gives the disputed term its plain and ordinary meaning and should be adopted.

Again, Sarepta argues that the relevant claims require a specific order to the disputed terms. Like before, Sarepta's arguments rely on its assertion that the recitation of "said Compound 4" (or just "Compound 4" in claim 1) requires step f) to use the exact "Compound 4" that was identified in step e). Br. at 56-58. However, as Dr. Luedtke has explained, Sarepta is mistaken. Ex. 15 ¶¶28-30, 74-81. Compound 4 is defined and identified in the claims by its chemical structure not by the process used to form it:



'322 Patent, cl. 1. Step f)'s recitation of "Compound 4" or "said Compound 4" is simple antecedent shorthand used to identify that Compound 4 in step f) has the same chemical structure as Compound 4 that was previously defined. Ex. 15 ¶¶28-30, 74-81. For this reason, the language and structure of the claims does not require a specific order to the steps.

As previously stated, "[t]he transition 'comprising' in a **method claim** [as is used here] indicates that the claim is open-ended and **allows for additional steps.**" *Medichem*, 353 F.3d at 933 (emphasis added). Like with Term 2, "**[s]ince the claim is not foreclosed to additional steps, the steps themselves are not foreclosed from being carried out in a different order than stated in the claim.**" *Lincoln Nat'l*, 2007 U.S. Dist. LEXIS 16822, at \*35. As discussed above, the possibility of additional steps demonstrates that a specific order is not required:

Step Number	Method A (Only Claimed Steps)	Method B (Additional Unrecited Steps)
1	Step a) – Providing Compound 1	Step a) – Providing Compound 1
2	Step b) – Forming Compound 2	Step b) – Forming Compound 2
3	Step c) – Reacting Compound 2 with a monomer	Step c) – Reacting Compound 2 with a monomer
4	Step d) – repeating steps b) and c) to form Compound 3	Step d) – repeating steps b) and c) to form Compound 3
5	Step e) – Reacting Compound 3 with reagent to form Compound 4	Conducting a series of reactions (not a single reaction using a deprotecting agent) to form Compound 4.
6	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO	Step f) – Reacting Compound 4 with acid to form the Oligomer or PMO
7		Conducting a series of reactions to reform Compound 3
8		Step e) – Reacting Compound 3 with reagent to form Compound 4
9		Conducting a series of reactions (not a single reaction using an acid) to form the Oligomer or PMO.

Sarepta's rebuttal repeats its incorrect argument that the recitation of "said Compound" from the preceding step imports a claim order. Br. at 57-58.

Sarepta also argues that the specification supports a step order because the only embodiment in the specification recites an order—based on language that is not found in the claim. *Id.* at 56-57 (arguing that "sole synthesis scheme reported and exemplified in the specification also follows the precise order of steps" and noting that "the specification...instructs a skilled artisan to react Compound 4 'produced in' step e"). But it is "one of the cardinal sins of patent law [to read] a limitation from the written description into the claims." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001); *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000) ("[P]articulate embodiments appearing in a specification will not be read into the claims when the claim language is broader than such embodiments."); *GE Lighting*, 750 F.3d at 1308-10 ("[I]t is improper to read limitations from a preferred embodiment described in the specification—even if it is the only embodiment."). Accordingly, there is no basis to import Sarepta's requested step order into the claim.

Sarepta's proposed construction of Term 3 also includes a requirement that the two ingredients react "directly"—i.e., without any other reagents used as part of the reaction. Br. at 58-59. Sarepta's argument for the inclusion of "directly" in Term 3 must be rejected for the same reasons it was inappropriate to include "directly" in Term 2. *See* Section V.B.3.b. Moreover, as Dr. Luedtke explains, the '322 Patent expressly explains that step f) can be a multi-step reaction. Ex. 15 ¶¶67-71 (demonstrating that the '322 Patent describes step f) as including a multi-step reaction involving an acid treatment reaction and a neutralization reaction). Since Sarepta's proposed construction would exclude a preferred embodiment, it must be rejected. *GE Lighting*, 750 F.3d at 1311.

Finally, to the extent the Court agrees with Sarepta that NS's proposed construction “characterizes the PMO or oligomer as simply a goal of step f),” that was not NS's intent. Br. at 60. NS does not dispute that step f) must result in the formation of the oligomer or PMO. To the extent the Court believes that NS's construction is unclear in that respect, NS would be willing to adopt language confirming that the reaction of step f) “results in” the oligomer or PMO.

Since NS's proposed construction gives the disputed phrase its plain and ordinary meaning and Sarepta's proposed construction imports additional limitations contrary to claim construction principles, NS's proposed construction should be adopted and Sarepta's proposed construction should be rejected.

#### **4. Sarepta's Sur-Reply Position**

##### **a. Sarepta's Construction Conforms to the Intrinsic Evidence**

NS largely repeats the same erroneous arguments for step f) as for step e). Br. at 61-64. While NS again focuses on the “comprising” term (Br. at 62), the intrinsic evidence demonstrates that the claims require the specified order of steps, and that step f), which forms the claimed “oligomer” or “PMO,” is the final step. *See supra* § V.B.4.a. NS's attempt to rewrite “*said Compound*” as “*a Compound*” from any source (Br. at 61-62) is contrary to logic of the claims, which are directed to a sequential synthesis scheme, the claim language (which, in claim 6, recites “*said Compound*,” not “*a Compound*”), and the specification (which identifies step e) as the *sole* source for obtaining Compound 4). Ex. 2 at 23:1-57; *see supra* § V.B.4.a; Pentelute Rep. Decl. ¶¶49-55. NS's position is also legally incorrect, as confirmed by *Eastman, Mantech, Bio-Rad*, and *Amgen*, which held that analogous claim terms linked the recited steps in the order written. *See supra* § V.B.4.a.

NS alleges that Sarepta reads “the only embodiment” from the specification into the claims. Br. at 63. But the specification *confirms* the claims’ plain language, which requires performing the steps in the order written. *See supra* § V.B.4.a; Pentelute Decl. ¶¶71, 46-51.

NS also speculates that “step f) *can* be a multi-step reaction” and thus should not be limited to a *direct* reaction. Br. at 63. But the “multi-step” reaction identified by Dr. Luedtke (¶¶67-71) still involves *direct* reaction of Compound 4 with an acid, followed by non-transformative steps. Pentelute Rep. Decl. ¶¶56-58.

**b. NS’s Construction Is Impermissibly Broad**

NS’s construction omits the source of Compound 4, encompasses indirect reactions between Compound 4 and an acid, and allows performing step f) out of order. Ex. 2 at claim 6 (“reacting *said* Compound 4 *with* an acid”); *id.* at 23:1-57 (directly reacting Compound 4 from step e) with an acid); Pentelute Rep. Decl. ¶¶59-62. The Court should reject NS’s overbroad construction. *See Howmedica*, 822 F.3d 1312 at 1320-22.

Dated: March 20, 2023

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I, Amy M. Dudash, an attorney certify that on March 20, 2023, a true and correct copy of the foregoing document was filed and served on all counsel of record via CM/ECF.

*/s/ Amy M. Dudash*

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